

A review of cardiovascular toxicity of TiO₂, ZnO and Ag nanoparticles (NPs)

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Abstract To ensure the safe use of nanoparticles (NPs) in modern society, it is necessary and urgent to assess the potential toxicity of NPs. Cardiovascular system is required for the systemic distribution of NPs entering circulation. Therefore, the adverse cardiovascular effects of NPs have gained extensive research interests. Metal based NPs, such as TiO₂, ZnO and Ag NPs, are among the most popular NPs found in commercially available products. They may also have potential applications in biomedicine, which could increase their contact with cardiovascular systems. This review aimed at providing an overview about the adverse cardiovascular effects of TiO₂, ZnO and Ag NPs. We discussed about the bio-distribution of NPs following different exposure routes. We also discussed about the cardiovascular toxicity of TiO₂, ZnO

and Ag NPs as assessed by in vivo and in vitro models. The possible mechanisms and contribution of physicochemical properties of metal based NPs were also discussed.

Keywords Nanoparticles (NPs) · Bio-distribution · Cardiovascular toxicity · Oxidative stress · Inflammation

Introduction

The development of nanotechnologies has deeply changed the whole world. Many engineered nanoparticles (NPs) are produced and used to utilize their unique properties owned by materials at nanoscale, making NPs as a major source for particle exposure in modern society (Boyes et al. 2017; Wu and Tang 2018). Of them, metal based NPs have gained extensive attention because they could be used not only in industry for optical, electrical, magnetic applications (Zhang et al. 2017b; Yang et al. 2017; Gong et al. 2017), but also in biomedicine for bio-imaging (Xu et al. 2016; Zhao et al. 2016), disease treatment (Tian et al. 2015; Liu et al. 2010) and antimicroorganisms (Chen et al. 2012, 2014b). Indeed, metal based NPs are the most popular NPs found in commercially available products, as revealed by a recent survey (Vance et al. 2015). As such, exposure of human beings to metal based NPs is increasing and

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there is an urgent need to assess the potential adverse health effects.

The adverse health effects of metal based NPs to cardiovascular systems have gained extensive research interests in recent years. For one thing, due to their relatively small sizes metal based NPs are able to cross physiological barriers and consequently enter blood stream (Frohlich and Roblegg 2016; Labouta and Schneider 2013). Therefore, it could be expected the metal based NPs will likely interact with cardiovascular system when human beings are exposed to NPs during production as well as daily uses. For another thing, the circulation system is required to deliver NPs to targets. This suggests that the potential effects of NPs to cardiovascular systems should be carefully assessed to ensure their safe use in biomedicine (Tomaszewski et al. 2015; Setyawati et al. 2015).

The aim of the present review is to provide an overview about the toxicity of the most popular metal-based NPs to cardiovascular systems. These NPs include Ag, TiO₂ and ZnO NPs (Vance et al. 2015). We discussed the bio-distribution of these NPs as assessed by different models and exposure routes. We also discussed about the cardiovascular toxicity of metal-based NPs to animals and cells in cardiovascular system as well as the possible mechanisms. We also discussed about the role of physicochemical properties in defining the cardiovascular toxicity of metal based NPs. It is our hope that this review may help future studies in this area.

Bioavailability and bio-distribution of metal based NPs

Regardless of exposure routes, the vascular system is responsible for distribution of NPs in circulation, and it is important to study the preferential accumulation and distribution sites following NP exposure. Several studies have addressed the issue of bioavailability and bio-distribution of metal based NPs. For ZnO NPs, pilot studies showed that following oral exposure, fluorescent ZnO NPs could be found in blood and distributed to various organs (for example livers, bones and brains) rapidly in mice or rats (Lee et al. 2012a, b; Li et al. 2012). Yang et al. (2014) investigated the bio-distribution of ZnS and ZnO quantum dots (QDs), and it was shown that QDs

through intravenous administration mainly trapped in the lung and liver of mice, and could be rapidly (within 1 h) removed from blood. By the measurement of Zn elements, Wang et al. (2016) observed significant accumulation of Zn in livers, pancreas, kidneys and bones of mice after long term consumption of ZnO NP containing diets, which caused developmental toxicity. Similarly, Chen et al. showed that tongue instillation of ZnO NPs to rats led to accumulation of Zn elements in brains, which is associated with damages to central nervous systems and impaired learning and memory (Aijie et al. 2017). The same group also found that exposure of pregnant rats to ZnO NPs by gavage resulted in accumulation of Zn elements in offspring brains, which may consequently cause impaired learning and memory capabilities in adulthood (Xiaoli et al. 2017). Kielbik et al. (2017) recently investigated the bio-distribution and elimination of biodegradable Eu doped ZnO NPs, and it was shown that following intragastric administration, biodegradable ZnO NPs could efficiently cross physiological barriers and accumulate in various organs of mice (3 h post exposure). In addition, NPs could also be eliminated primarily by livers and kidneys. In another study, Park et al. (2017) showed that ZnO NPs coated with phosphate and sulfide were mostly distributed in the spleen and thymus, which influenced the immune regulation function of mice. Chen et al. (2015a) developed pharmacokinetic model to describe the dynamic interactions of ZnO NPs in mice, and suggested that ZnO NPs with different sizes could be distributed to different organs but eliminated in livers and gastrointestinal tract. However, the smaller NPs tend to accumulate in body for a relatively longer time. In combination, these studies suggested that ZnO NPs as partially soluble NPs could be adsorbed and distributed to various organs when they enter vascular systems.

Similar to ZnO NPs, Ag NPs are also partially soluble to release Ag ions. Smulders et al. (2014) found that oropharyngeal aspiration of mice to Ag NPs resulted in Ag bio-distribution not only in lungs, but also in systemic organs such as heart, liver, spleen and kidney. Yun et al. (2015) found systemic bio-distribution of Ag in rats following oral exposure, which could be responsible for the liver and kidney toxicity. For comparison, exposure to SiO₂ and Fe₂O₃ NPs showed almost no systemic distribution. Similarly, Hendrickson et al. (2016) also found that intragastrical

administration of rats to Ag NPs resulted in Ag accumulation in the liver, kidneys, spleen, stomach, and small intestine, but most of the NPs were efficiently excreted from organs. Martins et al. (2017) recently showed Ag element distribution in an order of blood > liver > kidneys in rats after oral exposure. For intravenous administration, Su et al. (2014) showed Ag NPs firstly accumulated predominantly in liver and spleen, and then dissolved and release Ag ions to accumulate in other organs. Pang et al. (2016) showed surface chemistry dependent bio-distribution and systemic toxicity of Ag NPs in mice following intravenous injection. Bachler et al. (2013) developed pharmacokinetic model, and suggested that Ag NPs could be distributed and stored in systemic organs as insoluble NPs than dissolve into Ag ions. Combined, these studies indicated relatively high bioavailability and bio-distribution of Ag NPs.

Unlike the mentioned NPs above, TiO₂ NPs almost seldom dissolute. However, systemic bio-distribution of TiO₂ NPs could still occur via different exposure routes. Kreyling et al. (2017) recently compared different biokinetics patterns of TiO₂ NPs after oral, inhalational and intravenous exposure, and results showed that NPs could be distributed to secondary organs in rats. In addition, the biokinetics patterns following intratracheal instillation and gavage were similar but differed distinctly from the pattern after intravenous injection. Wang et al. (2013) found Ti accumulation in blood, liver, kidney and spleen of both young and adult rats after oral exposure, but young rats were more sensitive to NP induced injury. Bachler et al. (2015) have developed physiologically based pharmacokinetic model, and indicated that TiO₂ NPs following oral exposure were able to cross the capillary wall of the organs and to be phagocytosed by macrophages. Gate et al. (2017) recently found that TiO₂ NPs after inhalational exposure were slowly cleared from rat lung, which might translocate and accumulate in spleen and liver but not kidney or brain. However, Chen et al. found that tongue instillation of TiO₂ NPs to rats led to Ti biodistribution to brains, which induced adverse effects to central nervous systems (Aijie et al. 2017). Disdier et al. (2015) also found that TiO₂ NPs after intravenous administration could translocate to rat brain. Moreover, Ti in liver, lungs and spleen could be persisted up to 1 year after NP administration. Elgrabli et al. (2015) found that intravenous administration of TiO₂ NPs accumulated

in liver, lungs and spleen of rats, with a half life in the body to about 10 days. All of these studies suggested that TiO₂ NPs as insoluble particles could be distributed and accumulated in various organs following oral, inhalational and intravenous exposure.

To summarize from this part, previous studies have revealed the bio-distribution and accumulation of ZnO, Ag and TiO₂ NPs in systemic organs via different exposure routes (Table 1). Since the vascular circulation is required for bio-distribution of NPs, this suggests that metal based NPs will likely interact with blood cells during daily and medicinal uses. Therefore, it is necessary and important to investigate the adverse effects of metal based NPs to cardiovascular systems.

Cardiovascular toxicity of metal based NPs

Evidences from in vivo studies

The cardiovascular toxicity of metal based NPs has been assessed in normal or diseased laboratory animals. For ZnO NPs, a pilot study showed oral exposure of rats to ZnO NPs induced elevation of serum inflammatory mediators as well as tissue damages to hearts, which could be significantly alleviated by antioxidants (Baky et al. 2013). A recent study also showed that intratracheal instillation of normal rats to ZnO NPs could induce dyslipidemia, elevation of inflammatory markers in serum, and atherosclerotic alterations (such as vessel wall thickness, endothelial damage and migration of smooth muscle cells to the intima layer), which were similar or even stronger compared with the effects of high fat diet. In supportive of in vivo findings, in vitro exposure of A549 epithelial layers to ZnO NPs led to over-expression of HO-1 and PECAM-1 in human coronary artery endothelial cells of a co-culture model, which could be the mechanism associated with atherosclerotic alterations (Yan et al. 2017). In another study, it was shown that oropharyngeal aspiration of ZnO NPs in brain and muscle ARNT-like protein-1 knockout mice was procoagulant with a significant increase of coagulation factor FVIII. However, unlike carbon nanotubes which induced inflammatory responses and oxidative stress in lungs, exposure to ZnO NPs was associated with reduced inflammatory responses and oxidative stress, which

Table 1 The bio-distribution of ZnO, Ag and TiO₂ NPs in laboratory animals

NPs	Physicochemical properties	Exposure	Models	Bio-distribution	Reference
ZnO	20, 100 nm	Oral exposure, 250 mg/kg	Female BALB/c mice	Bone, liver, brain, lung, kidney, GI tract	Lee et al. (2012a)
ZnO	20, 100 nm	Oral exposure, 250 mg/kg	SD rats	Lung, liver, kidney, GI tract	Lee et al. (2012b)
ZnO	~ 50 nm	Fed or IP injection, 2.5 g/kg	Male Crl:CD-1 mice	Liver, spleen, kidney, heart, lung, testes	Li et al. (2012)
TiO ₂	Average size 75 ± 15 nm, hydroxyl groups on surface	Oral exposure, 10, 50, 200 mg/kg for 30 days	SD rats (young and adult)	Liver, kidney, spleen	Wang et al. (2013)
Ag, TiO ₂	TiO ₂ 15 nm, Ag 25–85 nm	Oropharyngeal aspiration of 20 µg, once a week for 4 weeks	BALB/c mice	TiO ₂ : lung; Ag: lung, liver, spleen, kidney, heart	Smulders et al. (2014)
Ag	Average size 35.3 ± 8.2 nm	IV injection, 125 µg	Male SD rats	Liver, spleen, lung, brain, kidney	Su et al. (2014)
ZnS, ZnO QD	ZnS QD 4.2 nm; ZnO QD 5.4 nm	IV injection, 2, 6, 20 mg/kg	Male Kunming mice	Lung, liver, spleen, kidney	Yang et al. (2014)
TiO ₂	Average size 21.5 ± 7.2 nm	IV injection, 1 mg/kg	Male Fisher F344 rats	Liver, lung, spleen, kidney, brain	Disdier et al. (2015)
TiO ₂	< 25 nm, anatase	IV injection, 1.7 mg/rat	Male SD rats	Liver, lung, spleen	Elgrabli et al. (2015)
Ag	11 nm, citrate-capped	Oral exposure, 2061 mg/kg (acute), 515.3, 1030.5, 2061 mg/kg (14-day repeated)	SD rats	Liver, lung, spleen, kidney, brain	Yun et al. (2015)
Ag	12 nm	Intragastric administration, 2000 mg/kg (single), 250 mg/kg for 30 days	Male rats	Liver, kidney, spleen, stomach, small intestine	Hendrickson et al. (2016)
Ag	~ 30 nm, citrate, PEG, PVP, BPEI coated	IV injection, 1 mg/kg	BALB/c mice	Liver, lung, spleen, kidney, brain, gut	Pang et al. (2016)
ZnO	Average size 40.90 ± 3.18 nm	Fed 50, 500 and 5000 mg/kg for 32 weeks	CD-ICR male mice	liver, pancreas, kidney, bone	Wang et al. (2016)
ZnO, TiO ₂	ZnO 50 nm, TiO ₂ 25 nm	Tongue instillation, 50 mg/kg, every other day for 30 days	Male Wistar rat	Brain	Aijie et al. (2017)
TiO ₂	P25, 21.5 ± 7.2 nm, 75% anatase, 25% rutile	Inhalational exposure to 10 mg/m ³ , 6 h/day, 5 day/week for 4 weeks	Male Fisher F344 rats (young and old)	Lung, spleen, liver	Gate et al. (2017)
ZnO	Eu doped, length 100–900 nm, width 70–300 nm	Intragastric administration of 3 mg/mouse	BALB/c mice	Duodenum, kidney, spleen, adipose tissue, skeletal muscle, bone	Kielbik et al. (2017)
TiO ₂	Median size 70 nm	IT instillation, 40–240 µg/kg	Female Wistar-Kyoto rat	Gut, liver, kidney, heart, spleen, brain, uterus	Kreyling et al. (2017)
Ag, TiO ₂	Ag 91.71 ± 1.6 nm; TiO ₂ 41.99 ± 1.63 nm	Oral gavage 0.5 mg/kg, daily for 45 days	Male Wistar rat	Liver, kidney	Martins et al. (2017)
ZnO	~ 50 nm, coated with phosphate and sulfide	Oral exposure of 0.5 and 1 mg/kg for 28 days	ICR mice	Thymus, spleen, brain, liver	Park et al. (2017)

Table 1 continued

NPs	Physicochemical properties	Exposure	Models	Bio-distribution	Reference
ZnO	50 nm	Intragastric gavage 500 mg/kg for 18 days	Pregnant SD rat	Heart, liver, kidney, brain	Xiaoli et al. (2017)

BPEI branched polyethyleneimine, *GI* gastrointestinal, *IP* intraperitoneal, *IV* intravenous, *NP* nanoparticle, *PEG* polyethylene glycol, *PVP* polyvinyl pyrrolidone, *SD* Sprague–Dawley, *QD* quantum dot

suggested that ZnO NPs and carbon nanotubes induced procoagulant effects via different mechanisms (Luyts et al. 2014). Recently, the possible cardiovascular toxicity to human beings was investigated, which showed concentration-dependent increase in symptoms, body temperature, acute phase proteins and neutrophils in blood of human volunteers following inhalational exposure to ZnO NPs. Because some of the elevated biomarkers are closely associated with atherosclerosis development, the authors suggested that inhalational exposure to ZnO NPs might promote cardiovascular diseases and should be limited (Monse et al. 2018). In contrast to the reports mentioned above, it has also been shown that injection of ZnO NPs in the left femoral artery did not dramatically influence hemodynamic parameters, leukocyte recruitment or thrombus formation in normal mice (Haberl et al. 2015). The different results obtained by different studies might be contributed to the models and exposure routes used.

For Ag NPs, it has been shown before that exposure of zebrafish embryos to Ag NPs, but not Au NPs at the same concentrations, led to a drop in heart rate, pericardial effusion, abnormal cardiac morphology and circulatory defects (Asharani et al. 2011). In a later study, it was also shown that early acute exposure of zebrafish embryos to Ag NPs induced a transient vascular endothelial growth factor (VEGF)-related gene expression and consequently delayed vascular development at later stages (Gao et al. 2016). These two studies suggested that early exposure of embryos to Ag NPs might impair the development of cardiovascular systems. In mice, a recent study showed that intravenous injection of Ag NPs at low levels decreased the heart rate, while at high levels induced sinus bradycardia, complete atrio-ventricular conduction block, and cardiac asystole. This was attributed to

direct effects of NPs on ion channels, as evidenced by that Ag NPs could decrease the Na⁺ currents, accelerated the activation, and delayed the inactivation and recovery of Na⁺ channels from inactivation in cultured mice cardiomyocytes (Lin et al. 2017). In rats, intratracheal instillation of Ag NPs resulted in expansion of cardiac ischemia–reperfusion injury and depression of the coronary vessel reactivity, which was likely associated with increases of circulating inflammatory mediators (Holland et al. 2015). In a later study, the same group further showed intratracheal instillation of rats to Ag NPs modestly increased serum cytokines as well as resulted in vascular dysfunction and exacerbated cardiac injury, and the extent of injury was correlated with capping agents and NP size (Holland et al. 2016). Exposure to Ag NPs has also been shown to induce the breakdown of blood brain barrier (BBB) and brain damage in both young and aged rats (Sharma et al. 2013). In later studies, the same group further showed that Ag NPs could exacerbate sleep deprivation induced brain damage as well as methamphetamine induced brain damage both in cold and hot environments (Sharma et al. 2015a, b). These studies in combination suggested that Ag NP exposure could lead to breakdown of BBB in vivo under different conditions.

In contrast to the mentioned studies, negative results have also been reported. For example, Roberts et al. (2013) found negligible changes of most of pulmonary or cardiovascular parameters in rats following inhalational exposure to wet silver colloid, although there was still modestly increased blood monocytes, decreased dilation of tail artery after stimulation, as well as elevated heart rate. Recently, Fennell et al. (2017) showed that administration of Ag NPs by intravenous injection or gavage to pregnant rats did not significantly elevated markers associated

with cardiovascular injury, although Ag NPs have been distributed to systemic organs. In healthy volunteers, oral exposure to commercial Ag particle solutions did not induce any adverse effects to cardiovascular systems and other systemic organs (Munger et al. 2014). The exact reasons that contributed to the positive and negative results in different reports remain unclear, but the exposure routes, models and physicochemical properties of NPs may have a role. The contribution of physicochemical properties of TiO₂, ZnO and Ag NPs in defining the cardiovascular toxicity will be discussed in later section. In addition, due to ethical reasons human beings could not be exposed to toxic NPs in controlled experiments. Therefore, although negative results have been reported in Ag NP exposed human volunteers (Munger et al. 2014), it may not completely conclude that Ag NPs are not toxic to humans and more studies are still needed to assert human toxicity thresholds.

For TiO₂ NPs, pilot study showed that injection of high levels of TiO₂ NPs into the abdominal cavity of mice led to damage of myocardium and disturbed serum balance of blood sugar and lipid, associated with an accumulation of small amount of Ti in hearts (Liu et al. 2009). Intraperitoneal injection of TiO₂ NPs also impaired heart function as well as induced pathological changes of myocardium, particularly when rats were simultaneously exposed to oxidative stress inducer alloxan (Sha et al. 2013). In another study, systemic administration of a single dose of TiO₂ NPs to mice significantly accelerated thrombus formation in the murine microcirculation, but this was only observed after exposure to TiO₂ anatase but not of TiO₂ rutile. In support of this, TiO₂ anatase but not TiO₂ rutile nanoparticles increased murine platelet aggregation *in vitro* (Haberl et al. 2015). These studies suggested that systemic exposure to high levels of TiO₂ NPs could be toxic to cardiovascular systems. For inhalational exposure, pilot study showed that aerosol inhalational exposure of rats to TiO₂ NPs promoted microvascular dysfunction, associated with increased oxidative/nitrosative stress and dismissed NO production (Nurkiewicz et al. 2009). In another study, intratracheal instillation of mice to TiO₂ NPs resulted in activation of complement cascade and inflammatory processes in heart as well as specific activation of complement factor 3 in blood, which was associated with a small translocation of NPs from

lungs (Husain et al. 2015). In pregnant rats, exposure to TiO₂ NP aerosols led to impaired endothelium-dependent dilation and active mechanotransduction in both coronary and uterine arterioles of the female offspring. In addition, there was also a reduction in maximal mitochondrial respiration in the left ventricle and uterus. These results indicated that prenatal TiO₂ NP exposure could lead to microvascular impairments, which might persist throughout multiple developmental stages (Stapleton et al. 2015). In atherosclerotic model ApoE^{-/-} mice, intratracheal instillation of a single dose of TiO₂ NPs promoted a modest increase in plaque progression in aorta but not vasodilatory dysfunction (Mikkelsen et al. 2011). Cardiovascular toxicity of TiO₂ NPs to ApoE^{-/-} mice was also confirmed by a later study, but the authors found that repeated intratracheal instillation of high levels of NPs significantly induced systemic inflammation, endothelial dysfunction, lipid metabolism dysfunction, finally leading to plaque progression (Chen et al. 2013). Repeated oral exposure of rats to TiO₂ NPs has also been shown to result in reduction of heart rate, injury of cardiac function as well as systemic inflammation (Chen et al. 2015b). Similarly, a recent study also showed that repeated oral exposure of TiO₂ NPs to normal rats led to histological changes in hearts and elevated oxidative stress and inflammatory markers in blood, which was alleviated by co-exposure to thymoquinone or avenanthramides due to their anti-oxidative and anti-inflammatory effects (Hassanein and El-Amir 2017). In early developing zebrafish embryos, exposure to high levels of TiO₂ ultra-small NPs (1–3 nm) showed anti-angiogenic effects and decreased NO concentration. TiO₂ ultra-small NPs at high concentrations also caused mortality and malformations in the form of pericardial edema. However, since *in vitro* study by using endothelial cells showed that TiO₂ ultra-small NPs were neither cytotoxic nor had oxidative ability, the authors suggested that the *in vivo* toxicity was probably induced by acidifying the water (Bayat et al. 2015). All of these studies in combination revealed cardiovascular toxicity of TiO₂ NPs *in vivo* to different models following different exposure routes.

To summarize from this part, previous studies have evaluated the *in vivo* cardiovascular toxicity of metal based NPs by different models and exposure routes (Table 2). The different models include normal animals, diseased animals as susceptible models, and

Table 2 Cardiovascular toxicity of ZnO, Ag and TiO₂ NPs as assessed by in vivo models

NPs	Physicochemical properties	Exposure	Models	Cardiovascular toxicity	Reference
TiO ₂	Anatase, 5 nm	IP injection of 5, 10, 50, 100, and 150 mg/kg daily for 14 days	Female CD-1 mice	Damage to myocardium, increased serum glucose and lipids	Liu et al. (2009)
TiO ₂	Fine TiO ₂ , ~ 1 µm; nano TiO ₂ , 21 nm	Inhalational exposure to 1.5–16 mg/m ³ particles for 240–720 min	Male SD rats	Microvascular dysfunction, ROS and decreased NO	Nurkiewicz et al. (2009)
Ag	5–35 nm, PVA coated	10, 25, 50, 75, 100 µg/mL	Zebrafish embryos	Decreased heart rate, abnormal cardiac morphology, circulatory defects	Asharani et al. (2011)
TiO ₂	Rutile fine TiO ₂ , 288 nm; photocatalytic 92/8 anatase/rutile TiO ₂ , 12 nm; rutile nano TiO ₂ , 21.6 nm	IT instillation of 0.5 mg/kg, once a week for 4 weeks	ApoE ^{-/-} mice	Plaque progression in aorta	Mikkelsen et al. (2011)
ZnO	50 nm	Oral exposure to 600 mg/kg, 1 g/kg for 5 days	Wistar albino rats	Increased serum inflammatory cytokines; DNA damage, caspase-3 activation, increased calcium concentration in hearts	Baky et al. (2013)
TiO ₂	Anatase, 5–10 nm	IT instillation of 10, 50, 100 µg, once a week for 6 weeks	ApoE ^{-/-} mice	Systemic inflammation, endothelial dysfunction, lipid metabolism dysfunction, increased plaque area and lipid-rich core area	Chen et al. (2013)
Ag	33 or 39 nm mean aerodynamic diameter	Inhalational exposure to wet Ag colloid for 5 h (estimated lung burdens 1.4, 14 µg Ag/rat)	Rats	Increased blood monocytes, decreased dilation of tail artery, elevated heart rate	Roberts et al. (2013)
TiO ₂	Nano TiO ₂ , rod like, 15 × 60 nm; micro, 1–5 µm	IP injection of 0.5, 5, 50 mg/kg	SD rats	Decreased heart function, pathological changes and oxidative damage in heart tissue	Sha et al. (2013)
Ag	20–30, 50–60 nm	50 mg/kg, IP injection once daily for 1 week	Male inbred SD rats (young and old)	Disruption of BBB and BCSFB, brain damage (old > young)	Sharma et al. (2013)
TiO ₂	P25 (80% anatase, 20% rutile, 21 nm)	Inhalational exposure (daily deposition 43.8 ± 1.2 µg) for 5 h per day, average 6.8 ± 0.5 days	Pregnant SD rats	Endothelial dysfunction in coronary and uterine arterioles, reduced maximal mitochondrial respiration in the left ventricle and uterus	Stapleton et al. (2015)
ZnO	100 nm	Oropharyngeal aspiration, once a week for 5 weeks, cumulative dose 32, 64 µg	Bmal1 ^{-/-} mice	Increased coagulation factor VII	Luyts et al. (2014)
Ag	Commercial Ag product (10 ppm, 5–10 nm; 32 ppm, 25–40 nm)	Oral exposure, 10 ppm for 3, 7, 14 days; 32 ppm for 14 day	Human volunteers	No significant effect in serum inflammation, oxidative stress, heart beat or morphological changes	Munger et al. (2014)

Table 2 continued

NPs	Physicochemical properties	Exposure	Models	Cardiovascular toxicity	Reference
TiO ₂	Rutile, 1–3 nm (ultra-small NPs); 30 nm (NPs)	100–1000 mg/L in water or 1 ng/embryo	Zebrafish embryos	Mortality, inhibited hatching, developmental abnormalities, increased Myo1c expression (ultra-small NPs only)	Bayat et al. (2015)
TiO ₂	24 ± 5 nm	Oral exposure of 2, 10, 50 mg/kg for 30 and 90 days	SD rat	Reduced heart rate, systolic blood pressure, increased diastolic blood pressure, injury of cardiac function, serum inflammation	Chen et al. (2015b)
TiO ₂ , ZnO, Ag	ZnO 150 nm; Ag 15 nm; TiO ₂ anatase 38 nm, rutile 67 nm	Injection of 1 mg/kg in left femoral artery	C57BL/6 mice	Thrombus formation (TiO ₂ anatase only)	Haberl et al. (2015)
Ag	20 nm, citrate coated	IT instillation of 0.2 mg	Male SD rat	Increased serum cytokines, cardiac ischemia–reperfusion injury, impaired vascular responsiveness	Holland et al. (2015)
TiO ₂	Average size 20.6 ± 0.3 nm	IT instillation of 18 and 162 µg	C57BL/6 mice	Complement cascade, inflammation in heart, complement factor 3 in blood	Husain et al. (2015)
Ag	20–30, 50–60 nm	50 mg/kg, IP injection once daily for 1 week	Male inbred SD rats (sleep deprivation)	Exacerbate disruption of BBB and BCSFB, brain damage	Sharma et al. (2015a)
Ag	50–60 nm	50 mg/kg, IP injection once daily for 1 week	Male inbred SD rats (hot and cold environments, METH treatment)	Exacerbate disruption of BBB and BCSFB, brain damage	Sharma et al. (2015b)
Ag	50 nm, PVP coated	0.1, 1.0, 10 mg/L	Zebrafish embryos/larvae	Transient VEGF related gene expression, delayed vascular development, and smaller larvae size at Hatching	Gao et al. (2016)
Ag	20 or 110 nm, citrate or PVP coated	IT instillation (200 µg for 1 day or 7 days)	Male SD rats	Increased serum cytokines, endothelial vasomotor dysfunction, cardiac ischemia reperfusion injury	Holland et al. (2016)
Ag	20 or 110 nm, PVP coated	IV injection, 1 mg/kg; gavage 10 mg/kg	Pregnant SD rat	No effect on cardiovascular injury	Fennell et al. (2017)
TiO ₂	21 nm	Oral exposure to 150 mg/kg for 6 weeks	Male SD rats	Histological changes in heart	Hassanein and El-Amir (2017)
Ag	75 nm, citrate coated	IV injection of 2, 3, 4, 6, and 8 mg/kg	Adult male C56BL6/J mice	Heart rate decrease, sinus bradycardia, complete atrio-ventricular conduction block, and cardiac asystole	Lin et al. (2017)

Table 2 continued

NPs	Physicochemical properties	Exposure	Models	Cardiovascular toxicity	Reference
ZnO	30 nm	IT instillation (0, 1.25, 2.5, and 5.0 mg/kg) once a week, 12 weeks	Male Wistar rats	Dyslipidemia (increased TC, LDL; decreased HDL); systemic inflammation (increased serum IL-8, TNF- α); atherosclerotic changes (increased HO-1, PECAM-1; aortic EC damage)	Yan et al. (2017)
ZnO	Mobility diameter \sim 10 nm	0.5, 1.0, 2.0 mg/m ³ for 4 h	Healthy human volunteers	Increased serum acute phase proteins and neutrophils	Monse et al. (2018)

ApoE apolipoprotein E, *BBB* blood–brain barrier, *BCSFB* blood-cerebrospinal fluid barrier, *Bmal1* brain and muscle ARNT-like protein-1, *EC* endothelial cell, *HDL* high-density lipoprotein, *HO-1* heme oxygenase-1, *IL-8* interleukin-8, *IP* intraperitoneal, *IT* intratracheal, *IV* intravenous, *LDL* low-density lipoprotein, *METH* methamphetamine, *NO* nitric oxide, *NP* nanoparticle, *PECAM-1* platelet endothelial cell adhesion molecules-1, *PVA* polyvinyl alcohol, *PVP* polyvinylpyrrolidone, *SD* Sprague–Dawley, *TC* total cholesterol, *TNF- α* tumor necrosis factor- α , *VEGF* vascular endothelial growth factor

more recently human volunteers, although due to ethical reasons there are only very limited human studies. The exposure routes include inhalational, oral and systemic exposure, which covers the main exposure routes in real life. Previous studies revealed various adverse cardiovascular effects associated with metal based NP exposure, such as endothelial dysfunction, heart tissue damage and elevated inflammatory markers in serum. However, negative results have also been reported, which suggested that the cardiovascular toxicity of metal based NPs still needs further investigations.

Evidence from in vitro studies

Human endothelial cells are commonly used to evaluate the toxicity of NPs entering circulation, since these cells are the surface cells covering the lumen of blood vessels (Cao et al. 2017a; Setyawati et al. 2015). Extensive studies have evaluated the toxicity of metal based NPs to human endothelial cells. For example, previous studies compared the cytotoxicity of several metal based NPs, and results showed that ZnO NPs were more cytotoxic to human endothelial cells compared with other metal based NPs such as Fe₃O₄, Al₂O₃, Ag and TiO₂ NPs (Danielsen et al. 2015; Sun et al. 2011; Gu et al. 2017). Liang et al. (2016) showed that ZnO NPs activated Fas death receptor pathway in human aortic endothelial cells, which led to apoptotic cell death. At non-cytotoxic concentrations, Ag NPs could also increase endothelial monolayer permeability by triggering vascular

endothelial cadherin phosphorylation at Y658 followed by VE-cadherin internalization (Sun et al. 2016). TiO₂ NPs have been shown to induce genotoxicity without cytotoxicity in human endothelial cells, which suggested that DNA damage might be more sensitive to reflect NP toxicity to endothelial cells (Bayat et al. 2015). In addition, direct exposure to ZnO, Ag and TiO₂ NPs could also induce endothelial dysfunction in vitro, showing as release of inflammatory cytokines, expression of adhesion molecules, adhesion of monocytes and eNOS uncoupling (Montiel-Davalos et al. 2012; Danielsen et al. 2015; Chuang et al. 2016; Suzuki et al. 2014; Shi et al. 2014). Combined, these results suggested that direct contact of endothelial cells with ZnO, Ag and TiO₂ NPs could be toxic.

Interestingly, the in vitro cardiovascular toxicity of metal based NPs was investigated not only in conventional endothelial cell mono-culture, but also in co-culture model based on endothelial cells. In a triple co-culture model of blood–brain barrier consisting of primary rat brain microvascular endothelial cells, pericytes and astrocytes, exposure of endothelial cells to Ag NPs led to increase of permeability as a result of decreased expression of the tight junction proteins and discontinuous tight junction proteins. Moreover, TEM images indicated that Ag NPs induced ultrastructural changes such as severe mitochondrial shrinkage, vacuolations and endoplasmic reticulum expansion (Xu et al. 2015a). In a similar co-culture model based on endothelial and astrocyte-like cells, it was shown that exposure to both Ag and TiO₂

NPs decreased transendothelial electrical resistance value and caused discontinuous tight junction proteins but did not induce the release of inflammatory cytokines (Chen et al. 2016). In the alveolar-endothelial co-culture model based on human coronary artery endothelial cells and human alveolar epithelial cell line A549, it was shown that exposure of A549 cells to ZnO NPs led to increased inflammatory mediators, HO-1 and PECAM-1 in the indirectly exposed endothelial cells. Pretreatment of A549 cells with the phagocytosis inhibitor blocked NP-induced toxicity in endothelial cells, which suggested that internalization of NPs into alveolar epithelial cells was required for the observed responses (Yan et al. 2017). In another study by using tri-culture model based on lung epithelial cell line NCI-H441 in the upper chamber and an immortalized pulmonary microvascular endothelial cell line (HPMEC-ST1.6R) and THP-1 cells in the lower chamber, it was shown that ZnO NP exposure did not significantly reduce the transepithelial electrical resistance but promoted the activation of endothelial cells, that the release of inflammatory cytokines was induced (Bengalli et al. 2017). These studies in combination suggested exposure to ZnO NPs could induce toxicity to endothelial cells not only in conventional mono-culture model, but also in the advanced co-culture model. These results also indicated possible signaling communications between NP directly and indirectly exposed cells.

Some studies also investigated the toxicity of metal based NPs to cardiomyocytes. A pilot study showed that TiO₂ NPs at high concentration (100 µg/mL) reduced contraction amplitude but did not significantly affect cellular survival or acute contractility at lower concentration (10 µg/mL) in rat cardiomyocytes. In the model of human cardiomyocytes, even 10 µg/mL of TiO₂ NPs reduced the beating rate significantly. These results suggested potentially adverse effects of TiO₂ NPs for myocardial tissue engineering applications (Jawad et al. 2011). Similarly, reduced action potential duration, impairment of sarcomere shortening and decreased stability of resting membrane potential was also observed in rat cardiomyocytes after in vitro exposure to TiO₂ NPs, which suggested that acute exposure to TiO₂ NPs might increase the likelihood of arrhythmic events (Savi et al. 2014). However, in a later study, it was shown that titanate nanotubes either functionalized with PEI or unfunctionalized could be internalized

into rat cardiomyocytes without obvious cytotoxicity, which suggested that titanate nanotubes could be safer nanocarriers for biomedical applications (Papa et al. 2013). Recently, it was shown that Ag NP exposure decreased the Na⁺ currents, accelerated the activation, and delayed the inactivation and recovery of Na⁺ channels in cultured mice cardiomyocytes. Ag NP exposure also rapidly decreased the inwardly rectifying K⁺ currents (IK1) and delayed the activation of IK1 channels. However, Ag NPs did not induce ROS and only mildly induced lactate dehydrogenase release. The authors suggested that Ag NP exposure could exert rapid toxic effects on myocardial electrophysiology without inducing ROS or membrane injury (Lin et al. 2017). At present relatively few studies investigated the influence of metal based NPs to cardiomyocytes, and more studies are needed to further confirm the toxicity of NPs to heart cells in vitro.

To summarize from this part, in vitro studies showed that ZnO, Ag and TiO₂ NP exposure could induce endothelial damage as well as endothelial activation not only in conventional endothelial cell culture, but also in co-culture model based on endothelial cells. Moreover, some studies also showed that these NPs could induce injury to cardiomyocytes and impair their physiological functions (Table 3). These results supported the in vivo observations that exposure to ZnO, Ag and TiO₂ NPs could be toxic to cardiovascular systems.

Mechanisms

Oxidative stress

Generally, NPs including ZnO, Ag and TiO₂ NPs, are chemically active which could induce ROS and oxidative damage to lipids, proteins and DNA of cardiovascular systems (Liang et al. 2016; Sun et al. 2016; Danielsen et al. 2015; Hassanein and El-Amir 2017; Sha et al. 2013). Moreover, an oxidative milieu due to metal based NP exposure could also lead to eNOS uncoupling, which in turn generate oxidants rather than NO (Montiel-Davalos et al. 2012; Chuang et al. 2016; Bayat et al. 2015; Baky et al. 2013). The role of oxidative stress in metal based NP induced cardiovascular toxicity was further confirmed by preventive studies using antioxidants. For example,

Table 3 Cardiovascular toxicity of ZnO, Ag and TiO₂ NPs as assessed by in vitro models

NPs	Physicochemical properties	Exposure	Models	Cardiovascular toxicity	Reference
TiO ₂	P25 (21 nm, 80% anatase, 20% rutile)	10, 100 µg/mL for 20 min, 2, 4, 24 h	Adult rat ventricular cardiomyocyte, hESC-CM	Reduced beating rate and contraction amplitude	Jawad et al. (2011)
ZnO	45.3 nm	0.001, 0.01, 0.1, 1, 5, 10, 20, 50, 100 µg/mL for 12 h or 24 h	HCMEC	Cytotoxicity, ROS, increased permeability, gene expression of adhesion molecules and IL-8	Sun et al. (2011)
TiO ₂	< 50 nm	5, 10, 20, 40 µg/cm ²	HUVEC	Inhibited proliferation, increased apoptosis, adhesion molecules, monocyte adhesion, inflammatory proteins, ROS and NO	Montiel-Davalos et al. (2012)
Titanate nanotube, TiO ₂	Nanotube: 10 nm diameter, functionalized with PEI nor not; NP: P25 not characterized	0.4, 1, 2, 5, 10 µg/mL for 24 h	Neonatal rat cardiomyocyte	Internalization without toxicity	Papa et al. (2013)
TiO ₂	25–35 nm, mixture of anatase and rutile	5, 25, 50 µg/mL for 1 h	Adult rat cardiomyocyte	Reduced action potential duration, impaired sarcomere shortening, decreased stability of resting membrane potential	Savi et al. (2014)
Ag	65 nm	0.5, 1, 1.5, 2.0, 2.5 µg/mL for 24 h	HUVEC	Cytotoxicity, apoptosis, increased ROS, inflammatory cytokines, adhesion molecules, monocyte adhesion	Shi et al. (2014)
TiO ₂ , ZnO	TiO ₂ 21 nm; ZnO 20 nm	1, 10, 25, 50, 100 µg/mL for 24 h	HUVEC	Cytotoxicity, adhesion molecule, monocyte adhesion (ZnO NP only)	Suzuki et al. (2014)
TiO ₂	Rutile, 1–3 nm (ultra-small NPs); 30 nm (NPs)	0.3, 0.6, 1.25, 2.5, 5, 10, 20, 40 µg/mL for 24 h	HMEC-1	DNA damage, decreased angiogenic activity, decreased NO	Bayat et al. (2015)
TiO ₂ , ZnO, Ag	TiO ₂ : 10 nm, 94 nm (rutile; positive, negative, neutral), 7 nm (anatase; neutral); ZnO: 100 nm (pristine), 130 nm (hydrophobic); Ag: < 20 nm	2, 4, 8, 16, 32, 64, 128, 256 µg/mL for 24 h	HUVEC	Cytotoxicity, ROS, inflammatory genes, adhesion molecules, monocyte adhesion	Danielsen et al. (2015)
Ag	7 ± 2 nm	1, 10 µg/mL for 24 h	Rat brain microvascular endothelial cell, pericyte, astrocyte co-culture	Increased endothelial permeability, astrocyte damage, changed expression of genes related with oxidative stress, inflammation, apoptosis	Xu et al. (2015a)
TiO ₂ , Ag	TiO ₂ 6, 35 nm; Ag 8 nm	TiO ₂ 100 ppm; Ag 4 ppm for 24 h	bEnd.3 endothelial cell and astrocyte like cell co-culture	Decreased viability, increased ROS, cytokine release, permeability	Chen et al. (2016)

Table 3 continued

NPs	Physicochemical properties	Exposure	Models	Cardiovascular toxicity	Reference
ZnO	20, 90 nm	20, 50, 150 µg/mL for 0.5, 1, 4, 6, 12, 24, 48 h	HCAEC	Decreased viability, increased 8-OHdG, IL-6, NO; decreased cardiovascular-associated gene expression	Chuang et al. (2016)
ZnO	20 nm (diameter)	8, 15, 25, 50 µg/mL for 12–24 h	HAEC	Cytotoxicity, ROS, apoptosis, MMP collapse	Liang et al. (2016)
Ag	~ 20 nm	2, 4, 6, 8, 10 µg/mL for 1 h	HUVEC	Increased permeability, vascular Endothelial-cadherin phosphorylation	Sun et al. (2016)
ZnO	Average diameter 38.3 ± 0.4 nm	1, 5, 10, 15, 20, 25 µg/mL for 24 h	HPMEC-ST1.6R and NCI-H441 co-culture	Release of inflammatory cytokines, adhesion molecules	Bengalli et al. (2017)
TiO ₂ , ZnO	7 nm, anatase (TiO ₂); 100 nm (ZnO)	2, 4, 8, 16, 32 µg/mL for 24 h	HUVEC	Cytotoxicity, increased ROS and Zn ions (ZnO NPs only)	Gu et al. (2017)
Ag	75 nm, citrate coated	0.1, 1, 10, 100, 1000 ng/mL for 5 min	Mice cardiomyocytes	Impaired activation of Na ⁺ /K ⁺ channels, loss of cell excitability, mild LDH release	Lin et al. (2017)
ZnO	30 nm	0, 12.5, 25, 50, 100, and 200 µg/mL for 24 h	A549-HCAEC co-culture	Cytotoxicity, release of IL-8 and TNF-α, HO-1 and PECAM-1 expression	Yan et al. (2017)

8-OHdG 8-Hydroxy-2'-deoxyguanosine, HO-1 heme oxygenase-1, HAEC human aortic endothelial cell, HCAEC human coronary artery endothelial cell, HCMEC human cardiac microvascular endothelial cell, hESC-CM human embryonic stem cell-derived cardiomyocyte, HMEC-1 human dermal microvascular endothelial cell line, HUVEC human umbilical vein endothelial cell, IL-8 interleukin-8, LDH lactate dehydrogenase, MMP mitochondrial membrane potential, NO nitric oxide, NP nanoparticle, PECAM-1 platelet endothelial cell adhesion molecules-1, ROS reactive oxygen species, TNF-α tumor necrosis factor-α

Liang et al. (2016) showed that ZnO NP exposure induced ROS and consequently triggered a decrease in mitochondria membrane potential, increase in Cyt-C release, activation of caspase 3 and caspase 9 and increase in the ratio of Bax/Bcl-2, which finally led to apoptosis of human endothelial cells. Furthermore, the antioxidant α -lipoic acid successfully protected endothelial cells from NP induced apoptosis. Shi et al. (2014) showed that Ag NPs could inhibit proliferation, damage the cell membrane, induce apoptosis, promote the up-regulation of inflammatory cytokines and adhesion of monocytes to endothelial cells. All of these responses were effectively antagonized by the antioxidant α -lipoic acid. Under in vivo conditions, Baky et al. (2013) found that co-administration of α -lipoic acid or vitamin E alleviated ZnO NP induced cardiovascular toxicity to rats. In another study, it was shown that TiO₂ NPs loaded with salvianolic acid B, a natural anti-oxidant, protected against myocardial damage caused by NP exposure in mice (Ding et al. 2016). These results suggested a role of oxidative stress in metal based NP induced cardiovascular toxicity, and alleviation of oxidative stress could be a possible way to reduce the adverse effects of metal based NPs to cardiovascular systems.

Modulation of inflammation

It is generally agreed that metal based NPs may modulate the immune function and influence inflammatory responses (Boraschi et al. 2017; Luo et al. 2015). Since cardiovascular diseases are typically associated with inflammatory responses, it is possible that metal based NPs could induce adverse cardiovascular effects due to the modulation of inflammation. For example, extensive studies by using endothelial cells showed that exposure to ZnO, Ag and TiO₂ NPs could promote cytokine release, expression of adhesion molecules, and monocyte adhesion (Danielsen et al. 2015; Chuang et al. 2016; Suzuki et al. 2014; Shi et al. 2014), which are key events associated with the development of cardiovascular diseases. Some studies suggested that endothelial activation after direct exposure to metal based NPs was due to the activation of transcription factor NF- κ B (Montiel-Davalos et al. 2012; Shi et al. 2014; Cao et al. 2017a). In laboratory animals, systemic administration of metal based NPs has been shown to induce inflammatory damage to cardiovascular systems (Haberl et al. 2015; Liu et al.

2009). Moreover, inhalational exposure to TiO₂ NPs resulted in low levels of translocation of NPs into cardiovascular systems, which in turn activated an early innate immune response essential for particle opsonisation and clearance (Husain et al. 2015). These results in combination with in vitro data suggested that direct contact of cardiovascular system with metal based NPs could induce cardiovascular toxicity associated with inflammatory responses. It appears that NP induced inflammation in cardiovascular systems is not necessary a result of inflammatory responses in the place of contact, because inhalational studies showed that metal based NPs promoted cardiovascular inflammation and damage without pulmonary inflammatory responses (Luyts et al. 2014; Mikkelsen et al. 2011). Interestingly, a recent study showed that inhalational exposure to ZnO NPs could elevate serum inflammatory markers in human beings. Since these markers are associated with the development of cardiovascular diseases, these results confirmed that exposure of human beings to metal based NPs might increase the risk of cardiovascular diseases through the modulation of inflammatory responses (Monse et al. 2018).

Dysfunction of autophagy

Autophagy is an evolutionarily conserved catabolic process where endogenous and foreign materials are sequestered in double-membrane vesicles for autophagic degradation in lysosomes, and convincing data indicated that non-biodegradable NPs could modulate autophagy and thus induce toxicological responses (Peynshaert et al. 2014; Anozie and Dalhaimer 2017). Some studies have also proved dysfunction of autophagy as the mechanisms for metal based NP induced cardiovascular effects. A pilot study showed that exposure to iron oxide and TiO₂ NPs led to DNA damage and provoked defensive mechanisms, which ultimately induced an autophagy process in human brain-derived endothelial cells (Halimoda et al. 2012). In another study, it was shown that Ag NPs promoted autophagy as increased LC3, which correlated with their cytotoxicity to human endothelial cells. Moreover, gene expression analysis confirmed autophagy and cell membrane damage-related necrosis as main toxicity pathways (Manshian et al. 2015). In a recent study, it was shown that the lysosomal deposition of CuO NPs led to lysosomal dysfunction, impairment of autophagic flux and the accumulation of

autophagosomes, which finally contributed to the cytotoxicity of NPs to human endothelial cells (Zhang et al. 2018). Similarly, in THP-1 monocytes it was shown that Ag NPs in lysosomes decreased lysosomal membrane stability, blocked autophagic flux and consequently impeded monocyte-macrophage differentiation, a crucial process involved in the development of cardiovascular diseases (Xu et al. 2015b). Indeed, there have been convincing data showing that dysfunction of autophagy is involved in NP induced toxicity to human endothelial cells (Cao 2018). Still, how NPs modulate autophagic pathway to induce toxicity is largely unknown and requires further studies (Anozie and Dalhaimer 2017).

Endoplasmic reticulum (ER) stress

Endoplasmic reticulum (ER) is a crucial organelle involved in proper protein folding, and accumulation of misfolded proteins in the ER could lead to a condition termed as ER stress, which has been implicated in the development of human diseases (Oakes and Papa 2015). Recently, it has been shown that NPs, particularly metal based NPs, might induce ER stress dependent toxicity (Cao et al. 2017a, b). Some studies have also investigated ER stress as the mechanism for metal based NP induced cardiovascular effects. For example, Chen et al. (2014a) found that ZnO NPs activated ER stress responses in HUVECs before inducing apoptosis, which suggested that ER stress might be an earlier end point for ZnO NP induced cytotoxicity. Similarly, Simon et al. (2017) recently found that exposure to TiO₂ nanosheets, nanoneedles and isotropic NPs was associated with an induction of ER stress in HUVECs, which was correlated with NP induced cytotoxicity. However, Huo et al. (2015) found that intratracheal instillation of mice with Ag NPs induced ER stress primarily in livers but not arteries. Under in vitro conditions, exposure to Ag NPs was associated with ER stress in bronchial epithelial cells but not endothelial cells. Thus, it is possible that metal based NP induced ER stress is dependent on the types of NPs and models used for evaluation. Currently, relatively few studies considered ER stress as the mechanism for metal based NP induced cardiovascular effects, although ER stress has been convincingly shown to be related with the toxicity of NPs (Cao et al. 2017b). Given the importance of ER stress in the development of

cardiovascular diseases (Oakes and Papa 2015), more work is need in the future to investigate the association between ER stress and metal based NP induced cardiovascular effects.

Role of physicochemical properties of NPs

Composition

Several studies investigated the toxicity of different types of metal based NPs to cardiovascular cells. A pilot study showed that ZnO and Y₂O₃ but not Fe₂O₃ NPs induced a pronounced inflammatory response and expression of adhesion molecules in human aortic endothelial cells. In addition, ZnO NPs at high concentrations were also cytotoxic (Gojova et al. 2007). Similarly, a later study revealed that ZnO and CuO NPs were more cytotoxic and inflammatory to human cardiac microvascular endothelial cells compared with other metal oxide NPs, such as MgO, Al₂O₃, Fe₂O₃ and Fe₃O₄ NPs (Sun et al. 2011). Danielsen et al. (2015) showed that ZnO and Ag NPs were more cytotoxic to human umbilical vein endothelial cells compared with TiO₂ NPs, but the later ones induced comparable or even higher adhesion molecules. One study suggested that the higher toxicity of ZnO NPs to cardiovascular cells was attributed to their higher solubility compared with other types of metal based NPs, such as TiO₂ NPs (Suzuki et al. 2014). Ag and TiO₂ NPs with similar sizes could increase the permeability of co-culture model based on human brain endothelial cells and astrocytes, but Ag NPs were more efficient to penetrate the co-culture model. Moreover, Ag and TiO₂ NPs increased the permeability through different pathways, that Ag NPs induced endothelial monolayer disruption by ROS-induced cell death, whereas TiO₂ NPs disrupted it by cytokine secretion (Chen et al. 2016). In the model of confluent porcine brain microvessel endothelial cells, exposure to Ag and Cu but not Au NPs significantly increased the permeability and release of inflammatory cytokines (Trickler et al. 2014). Combined, these studies suggested an important role of NP composition in determining the cardiovascular toxicity. It also indicated that the cardiovascular toxicity of metal based NPs should be evaluated case by case.

Size

Some studies have investigated the role of sizes of metal based NPs in determining the cardiovascular toxicity. In human dermal microvascular endothelial cell line, exposure to both TiO₂ ultra-small NPs (1–3 nm) and NPs (30 nm) induced DNA damage to similar extent, but only the ultra-small NPs decreased angiogenic activity and NO production. In zebrafish model, TiO₂ NP exposure did not significantly affect the development, whereas ultra-small NPs increased mortality, inhibited hatching, as well as promoted developmental abnormality and the expression of Myo1C, a gene involved in glomerular development (Bayat et al. 2015). In an in vitro blood–brain barrier model being composed of endothelial and astrocyte-like cells, it was shown that the smaller TiO₂ NPs (6 nm) was more potent to penetrate compared with the larger ones (35 nm), although both of NPs induced comparable decrease of cellular viability in endothelial cells (Chen et al. 2016). In the model of porcine brain microvessel endothelial monolayer, exposure to smaller Ag NPs (25 and 40 nm), but not the larger ones (80 nm), significantly promoted the release of inflammatory mediators. Moreover, the smaller Ag NPs were more potent than the larger ones to increase the permeability (Trickler et al. 2014). Under in vivo conditions, the relationship between NP sizes and cardiovascular toxicity appeared to be more complex, but a recent study still showed that intratracheal instillation of smaller Ag NPs (20 nm) induced a stronger cardiac ischemia reperfusion injury compared with the larger ones (110 nm) in rats (Holland et al. 2016). Overall, these studies suggested that NP sizes were crucial to determine the cardiovascular toxicity (Cao et al. 2017a; Setyawati et al. 2015). Generally, the smaller metal based NPs have a relatively larger surface area and are more chemically active, which can make them more toxic compared with the larger ones (Kinnear et al. 2017).

Crystal structure

It has been suggested that crystal structure could critically define their toxicity. This is of particular importance to TiO₂ NPs, since TiO₂ NPs normally have different crystal structures, such as anatase and rutile (Song et al. 2015; Golbamaki et al. 2015). Haberl et al. (2015) compared the cardiovascular

toxicity TiO₂ NPs with different crystal structures. It was shown that systemic administration of TiO₂ anatase, but not of TiO₂ rutile, significantly accelerated thrombus formation in the microcirculation of mice. Moreover, TiO₂ anatase but not TiO₂ rutile increased murine platelet aggregation in vitro. By using human umbilical vein endothelial cells, Danielson et al. (2015) showed that TiO₂ anatase were more potent than TiO₂ rutile to induce adhesion molecules, although they did not promote monocyte adhesion. Simon et al. (2017) compared the toxicity of TiO₂ nanoneedles, titanate scrolled nanosheets, gel-sol-based isotropic NPs and P25 to human umbilical vein endothelial cells. It was shown that titanate scrolled nanosheets were the most toxic NPs among others, which was likely due to that internalization of nanosheets influenced intracellular calcium homeostasis and consequently induced a prolonged ER stress. In contrast, it has also been shown that titanate nanotubes could be internalized into cardiomyocytes without inducing obvious cytotoxicity, which suggested that they were safe nanocarriers for biomedical applications (Papa et al. 2013). Thus, it is possible that the crystal structures of metal based NPs could influence their toxicity to cardiovascular systems, which should be taken into account for future nanotoxicological studies.

Surface chemistry

The surface chemistry is an important factor to influence their interactions with biological molecules and cells (Docter et al. 2015; Zhang et al. 2017a). Some studies compared the toxicity of metal based NPs with different surface chemistry to cardiovascular systems. Manshian et al. (2015) compared the interactions between human umbilical vein endothelial cells and Ag NPs with identical core sizes but different surface coating. It was shown that coating with poly(ethylene glycol) (PEG) reduced their cellular uptake efficiency compared with NPs coated with mercaptoundecanoic acid (MUA) or dodecylamine-modified poly(isobutylene-alt-maleic anhydride) (PMA). As a result, PEG coated NPs displayed the lowest levels of toxicity, although they induced the highest levels of ROS. MUA coated NPs were the most cytotoxic, which caused autophagy, cell membrane damage, mitochondrial damage, and cytoskeletal deformations. In rats following intratracheal

instillation of Ag NPs, Holland et al. showed that polyvinylpyrrolidone capped 110 nm Ag NP was more capable of expanding cardiac ischemia reperfusion injury compared with citrate capped 110 nm ones. This tendency was more obvious when the exposed rats were rested for 7 days (Holland et al. 2016). In contrast, Danielsen et al. (2015) found that surface chemistry did not significantly affect the toxicity of metal based NPs to human umbilical vein endothelial cells, that TiO₂ NPs with positive, negative and neutral surface charge induced comparable cytotoxicity, ROS and adhesion molecule expression. Similar trend was also observed for ZnO NPs with or without hydrophobic surface coating. At present, relatively few studies evaluated the influence of surface chemistry on metal based NP induced cardiovascular toxicity, and more work in this direction is needed in the future.

Conclusion

ZnO, Ag and TiO₂ NPs are currently the most popular metal based NPs used in commercially available products, which could lead to the exposure of human beings to NPs in real life. The present review provided an overview about the bio-distribution, cardiovascular toxicity and mechanisms of these NPs. In addition, the role of physicochemical properties in NP induced cardiovascular toxicity was also discussed. Studies have shown systemic bio-distribution of ZnO, Ag and TiO₂ NPs after inhalational, oral and systemic administration, which suggested that these NPs could be distributed to various organs by cardiovascular systems regardless of exposure routes. Exposure to ZnO, Ag and TiO₂ NPs could induce toxicity to cardiovascular systems both in vivo and in vitro, which could be explained by oxidative stress, modulation of inflammation, dysfunction of autophagy and ER stress. The physicochemical properties, such as composition, size, crystal structure and surface charge, have been shown to critically influence the cardiovascular toxicity of metal based NPs. Therefore, during the production and uses of ZnO, Ag and TiO₂ NPs it is necessary to consider their toxicity to cardiovascular systems. Moreover, it is also necessary to further study the mechanisms and role of physicochemical properties in cardiovascular toxicity of ZnO, Ag and TiO₂

NPs as well as other metal based NPs to design safer NPs for biomedical applications.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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