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Review

Developmental impacts and toxicological hallmarks of silver nanoparticles across diverse biological models

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ABSTRACT

Silver nanoparticles (AgNPs), revered for their antimicrobial prowess, have become ubiquitous in a range of products, from biomedical equipment to food packaging. However, amidst their rising popularity, concerns loom over their possible detrimental effects on fetal development and subsequent adult life. This review delves into the developmental toxicity of AgNPs across diverse models, from aquatic species like zebrafish and catfish to mammalian rodents and *in vitro* embryonic stem cells. Our focus encompasses the fate of AgNPs in different contexts, elucidating associated hazardous results such as embryotoxicity and adverse pregnancy outcomes. Furthermore, we scrutinize the enduring adverse impacts on offspring, spanning impaired neurobehavior function, reproductive disorders, cardiopulmonary lesions, and hepatotoxicity. Key hallmarks of developmental harm are identified, encompassing redox imbalances, inflammatory cascades, DNA damage, and mitochondrial stress. Notably, we explore potential explanations, linking immunoregulatory dysfunction and disrupted epigenetic modifications to AgNPs-induced developmental failures. Despite substantial progress, our understanding of the developmental risks posed by AgNPs remains incomplete, underscoring the urgency of further research in this critical area.

1. Introduction

Engineered nanoparticles (NPs) with at least one dimension ≤100 nm display unique physicochemical and biological properties compared to their macro-scaled counterparts [1–3]. The limitation of traditional antibiotics in deactivating drug-resistant bacteria has spurred the exploration of safe and effective germicidal materials [4–8]. Among them, silver nanoparticles (AgNPs) have been reported to kill gram-negative and gram-positive bacteria potently due to their particle-specific characteristics and Ag ions released [9–13]. AgNPs belong to the noble metal nanomaterial family and have been commonly used in various fields, including medical equipment, household appliances, water treatment, and the food industry, due to excellent broad-spectrum antigerm effects [14–17].

Despite their widespread use as bactericidal agents, AgNPs pose significant environmental risks. During washing, AgNPs can dissolve into an aqueous medium from commercial fibers, increasing the risk of environmental release [18–23]. While most AgNPs are removed by sludge adsorption or chlorine precipitation in sewage treatment plants [24], unremoved AgNPs in wastewater can undergo oxidization, resulting in the generation of toxic Ag ions (Ag^+), which have certain detrimental eco-environmental consequences, such as exerting harm to aquatic organisms [25–27]. Furthermore, AgNPs can be transformed into low-solubility salts such as silver chloride (AgCl) and silver sulfide (Ag_2S) [24,28,29], which can accumulate via the food chain [24,30], and harm a wide range of organisms [31–33], including vulnerable populations such as elders and pregnant women. Embryos, fetuses, and infants lack a well-developed defense system, making them more susceptible to xenobiotics [34,35]. The increasing use of AgNPs-containing personal care products raises concerns about their potential developmental hazards at the maternal-fetus interface [36–39]. Consequently, a more profound comprehension of the risk assessment of AgNPs to the maternal-fetal axis and the damaging

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List of abbreviations

Xa	Active X chromosome
ATP	Adenosine triphosphate
APOs	Adverse pregnancy outcomes
BAX	BCL2-associated X protein
AgNPs-C	Citrate-coated AgNPs
dpf	Days post-fertilization
DOHaD	Developmental Origin of Health and Disease
ENSCs	Embryonic neural stem cells
ESCs	Embryonic stem cells
FGF	Fibroblast growth factor
fgf-18	Fibroblast growth factor-18
GD	Gestational day
G6PDH	Glucose-6-phosphate dehydrogenase
GSH	Glutathione
GSSG	Glutathione disulfide
GPx	Glutathione peroxidase
GAP-43	Growth associated protein-43
H3K27me3	Histone 3 lysine 27 trimethylation
hpf	Hours post-fertilization
H_2O_2	Hydrogen peroxide
Xi	Inactive X chromosome
Ifn-γ	Interferon-γ
Il-1β	Interleukin -1β
Il-6	Interleukin-6
LDH	Lactate dehydrogenase
L-DOPA	L-tyrosine to 3,4-dihydroxy phenylalanine
MDA	Malondialdehyde
mmp-9	Matrix metalloprotein-9
MAO-A	Monoamine oxidase A
myh	MutY DNA glycosylase
γ-H2AX	Phosphorylation of H2AX
PVP/PEI	Poly N-vinyl-2-pirrolidone/Polyethyleneimine
AgNPs-PVP	Polyvinylpyrrolidone-coated AgNPs
PD	Post-delivery day
PCNA	Proliferating cell nuclear antigen
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
AgCl	Silver chloride
Ag^+	Silver ions
AgNPs	Silver nanoparticles
Ag_2S	Silver sulfide
SD	Sprague-Dawley
SOD	Superoxide dismutase
MnSOD, SOD2	Superoxide dismutase [Mn], mitochondrial
TEM	Transmission Electron Microscopy
Tsix	TSIX Transcript, XIST Antisense RNA
Tnf-α	Tumor necrosis factor-α
TH	Tyrosine hydroxylase
VEGF	Vascular endothelial growth factor
XCI	X chromosome inactivation
Xist	X Inactive Specific Transcript
DHPA	3,4-dihydroxy phenyl acetic acid
8-oxoG	8-oxo-7,8-dihydroguanine
8-oxodG	8-oxo-7-hydrodeoxyguanosine

mechanisms involved is imperative.

Environmental risks associated with the widespread use of AgNPs must be carefully evaluated to protect human health and the environment. This review compiled previous findings on the developmental toxicity of AgNPs in various *in vivo* and *in vitro* models, including zebrafish, mammal rodents, and embryonic stem cells (ESCs). We discuss the long-term adverse effects on future generations, such as neurodevelopmental impairment [40–42], reproductive insufficiency [43,44], hepatotoxicity [45], cardiopulmonary malfunction [46], pancreatic and kidney damage [47], and immunometabolism disorders [48], as well as controversial results regarding fetal and offspring consequences [48,49]. The underlying hallmarks of AgNPs-induced developmental damage are also explored, including redox disequilibrium, inflammatory response, genetic materials lesions, and subcellular dysfunction. However, conclusive information regarding the developmental hazards of AgNPs remains limited, demanding urgent and extensive research endeavors to comprehensively ascertain these potential hazards.

2. Hazardous impacts of AgNPs on embryos

Studies have shown that exposure to AgNPs can lead to embryotoxicity in multiple model organisms. In mammals, resorbed embryos were identified in different strains, including C57BL/6, C57BL/6J, and Kunming mice [46,50,51]. Furthermore, studies have shown that AgNPs enter zebrafish embryos through passive transport and cause delayed embryonic development, larval deformity, and even death [52]. Therefore, it is crucial to consider the potential embryonic hazards of AgNPs in various model organisms to fully understand their ecological impacts.

2.1. Embryo resorption in mammal rodents

In C57BL/6 mice, nose-only inhalation of AgNPs at 640 μg m^{-3} increased the number of resorbed embryos [50]. Similarly, non-surgical intratracheal instillation of AgNPs at an average size of 10.4 nm significantly increased the embryo resorption rate in C57BL/6J mice [46]. Furthermore, Kunming mice administrated with AgNPs at 11.61 nm via tail vein injection showed a significant increase in the rate of embryo resorption [51]. Notably, a recent study found that commercial drugs of vaginal gels containing AgNPs impaired mammalian embryo development, despite no apparent impairments in the reproduction of ICR female mice, a mouse strain from the Institute of Cancer Research and therefore called ICR mice in short [53]. Additionally, AgNPs hindered the development of *in vitro* fertilization embryos in particle size- and dose-dependent manner [53]. Overall, exposure to AgNPs during pregnancy through various routes, such as pulmonary exposure or intravenous injection, can lead to embryotoxicity across different strains.

The evidence suggests that maternal exposure to AgNPs can lead to embryotoxicity in murine species. However, a comprehensive framework of exposure properties, including pathways, concentrations, and periods, has not yet been formulated. There are lingering questions regarding the particle characteristics and exposure profiles that are predominantly responsible for embryotoxicity. Moreover, it is unclear whether malignant outcomes are derived from paternal contact, periconceptional treatments, or a combination of both factors. Future investigations need to shed light on this question and provide a complete picture of the potential embryotoxicity of AgNPs. While the available evidence underscores the hazards of maternal exposure to AgNPs in embryos, further research is urgently needed to understand the underlying

mechanisms and develop appropriate measures to protect vulnerable populations.

2.2. Embryotoxicity of AgNPs in zebrafish and influencing factors

Zebrafish (*Danio rerio*) embryos are ideal models for the risk assessment of exogenous substances due to their transparency and rapid development [54–56]. AgNPs can passively permeate into the chorionic space through chorion pore canals and transport into the inner mass of zebrafish embryos and cause damage [52]. Even if no AgNPs are detected inside the embryo, complete coverage of the chorion surface can lead to sublethal or lethal consequences [57]. The embryotoxicity of AgNPs has also been shown in other aquatic organisms, such as medaka (*Oryzias latipes*) and catfish (*Clarias gariepinus*). A summary of the developmental defects in these aquatic organisms is provided in Fig. 1, Table 1, and Supplementary Tables S1–S2.

Intentional engineering of factory-enriched nanomaterials with different attributes has led to new types of NPs with unique characteristics and functionalization, such as small sizes with certain coatings [3,58]. Extraordinary physiochemical properties render distinct biological performances between AgNPs and their bulky counterparts. Numerous studies have investigated the embryotoxicity of AgNPs in zebrafish, and the toxicity depends on a variety of factors, including size, shape, and surface chemical residues, as well as the developmental stage of the embryo, the presence of chorion, and husbandry milieu.

2.2.1. Dosage level and dose-response relationship

A study reported that increasing concentrations of 5–46 nm spherical AgNPs led to a decrease in normally developmental embryos and an increase in viable deformed zebrafish, with dead embryos increasing significantly above a concentration of 0.19 nM [52]. Another study reported that 1–20 nm AgNPs exponentially increased the mortality rate of zebrafish embryos, where complete death of embryos occurred at 100 mg L^{-1}, highlighting the importance of dose/concentrations in intricate biological outcomes [59]. Even non-teratogenic levels of 0.3–3 ppm (mg L^{-1}) caused transient hyperactivity in photomotor responses of zebrafish after exposure to AgNPs averaged at 25 nm from 4 to 120 h post fertilization (hpf), particularly the neurobehavioral changes occurring at three days post fertilization (dpf) [60]. Nonteratogenic concentrations of AgNPs can cause transient behavioral alterations during development, such as hatching delays, developmental anomalies, and behavioral changes. As the doses increase, AgNPs provoke deformities and mortality [52,61,62].

These findings suggest that even low levels of AgNPs exposure can significantly impact zebrafish embryonic development, leading to deformities, hyperactivity, and mortality as the dosage level rises. Therefore, the dosage level significantly affects the toxicological consequences of AgNPs. Similar trends were observed in medaka [26,63], and catfish [64], with the toxic effects of AgNPs increasing dose-relatedly. It is important to consider the dosage level of AgNPs when evaluating their potential hazards to aquatic organisms.

2.2.2. The release of silver ions

Silver (Ag) ions released from AgNPs have been found to partially explain both the antibacterial effects and adverse effects of AgNPs. Studies have shown that different concentrations of Ag ions for a wide range can exhibit hierarchical degrees of threats to zebrafish embryos, with higher concentrations significantly causing hatching delays and higher reducing survival rates. A concentration of 3 μM significantly reduced the survival rate of zebrafish embryos, whereas 1 μM caused hatching delays without threatening survival. Swimming behavior was impacted at concentrations below 0.1 μM, whereas the hatching rate remained unaffected [65].

The toxicity attribution of AgNPs to the leakage of Ag ions, the NPs, or a combination of both remains mysterious. However, adverse impacts of AgNPs appear to be closely associated with Ag ions [66–69]. Studies have reported that equal-amount dissolved ions are more toxic than particulate forms, and Ag ions could be highly accountable for adverse outcomes, such as hatching delays, morphological aberrations, and neurodevelopmental toxicology [70,71]. Furthermore, surface coating/functionalization and Ag ions chelation have effectively neutralized hypopigmentation [72], lethality, and phenotypic deformities [73], suggesting that Ag ions might primarily mediate the deleterious consequences of AgNPs.

While a series of research sustained that particulate is the main

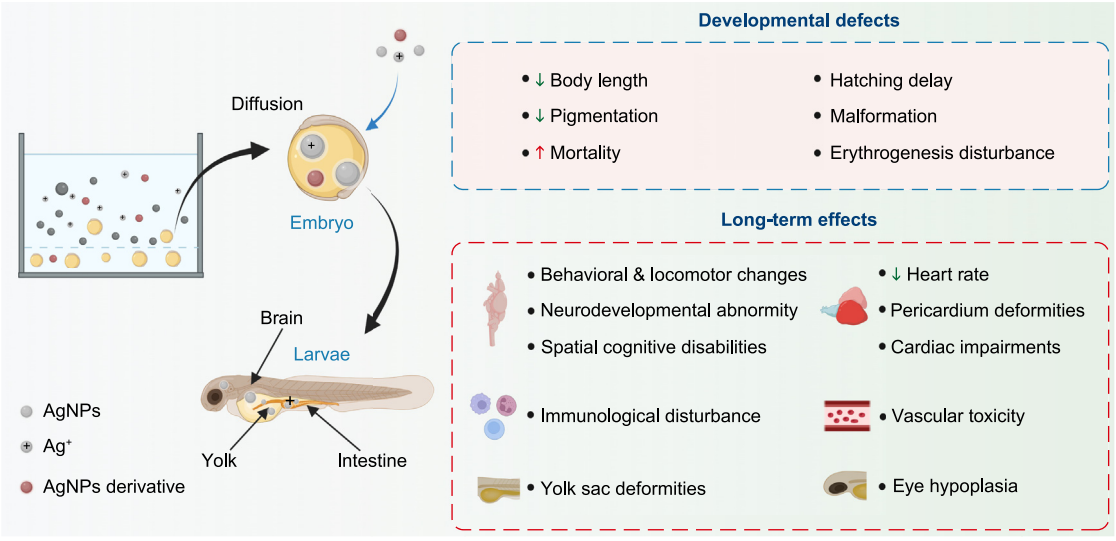

Fig. 1. Developmental hazards of AgNPs in zebrafish. Embryonic exposure to AgNPs can induce hatching delay, malformation, depigmentation, and even death. Long-term developmental defects mainly include cardiovascular damage, immunological disturbance, neuromotor disorders, and hypoplasia. Abbreviations: Nanosilver/silver nanoparticle (AgNPs). Symbols: ↓ denotes decrease; ↑ represents increase.

Table 1
Embryotoxicity of AgNPs on aquatic species zebrafish.

NPs	Size	Dose	Exposure period	Assay involved	Outcomes	Influential factors	Reference
Four different AgNPs, 20 or 110 nm in size, with polypyrrolidone (PVP) or citrate (C) surface coatings	20 and 100 nm	0.8, 4, 20, 10, and 50 mg L^{-1}	6–24 hpf; 6–120 hpf	Twenty-two endpoints, including mortality and malformation.	Particle size, particle agglomeration, and chorion interference are responsible for the mortality and malformation of embryos; Embryonic toxicity in the absence of chorion was greater than in its presence; The smaller 20-nm AgNPs were more toxic than the larger 110-nm AgNPs; When the agglomeration was controlled, or in the presence of chorion, AgNPs-PVP were more toxic than AgNPs-C.	Particle size, coatings, and chorion	[61]
AgNPs	97 ± 13 nm	(2, 4, 8, 16, and 24 pM) or (6.03, 12.06, 24.12, 48.24, and 72.36 mg L^{-1})	2 h (specific stage of embryos I–V, acute treatment)	A quantitative study of the toxicity of AgNPs; Imaging and characterization of AgNPs embedded inside zebrafish.	Stage I (the cleavage stage) is the most sensitive to AgNPs; The earlier developmental stage embryos are much more sensitive to the effects of the NPs than the later stage embryos; Embryonic phenotypes strikingly depend on the sizes and embryonic developmental stages.	Stage of embryonic development	[94]
AgNPs	13.1 ± 2.5 nm	(0.02, 0.04, 0.05, 0.06, 0.07, 0.2, 0.4, 0.5, 0.6, and 0.7 nM) or (0.15, 0.3, 0.37, 0.45, 0.52, 1.34, 2.6, 3.94, 4.61, and 4.9 mg L^{-1})	2 h (specific stage of embryos I–V, acute treatment)	*In vivo* real-time imaging of diffusion and transport of single Ag-peptide NPs into/in embryos; Quantitative imaging and analysis of single Ag-peptide NPs embedded in zebrafish.	The stage IV late-segmentation embryos are the most sensitive, while the stage V hatching embryos are most resistant to AgNPs; AgNPs passively diffused through the chorion layers into various developmental stages of embryos via chorionic pores, in the chorion space, and into the inner mass embryos; Unambiguous stage- and dose-dependent toxic effects on embryonic development; The embryos treated with the NPs showed a wide variety of abnormalities.	Stage of embryonic development	[95]
AgNPs	12 and 21 nm	0.02, 0.04, 0.06, 0.1, and 0.14 mg mL^{-1}	From 24 or 48 hpf to hatching	Metabolic processes oxygen consumption; Respiration rate measurement.	12 nm particles were found to be more bioactive than 21 nm; Above 0.01 mg mL^{-1}, both sizes decreased embryo survival; Surface area is a more significant determinant of particle toxicity than mass or particle numbers.	Size, dose, and surface area	[88]
AgNPs	41.6 ± 9.1 nm	0.02, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.7 nM	10, 24, 48, 72, 96, and 120 hpf	Real-time tracking of diffusion of single AgNPs into/in embryos; Dose-dependent biocompatibility and toxicity experiments; Quantitative characterization of single AgNPs embedded in individual zebrafish.	At the same molar concentration, larger AgNPs (41.6 ± 9.1 nm) are more toxic than the smaller (11.6 ± 3.5 nm); 30–72 nm passively diffused into the embryos through chorionic pores via random Brownian motion and stayed inside the embryos throughout their entire development; 0.02–0.2 nM increases the number of deformities, while higher than 0.2 nM, all embryos became dead; Malformations include cardiac abnormalities, yolk sac edema, and eye/head abnormalities. Deformed zebrafish with a higher number of larger NPs, showing striking size-dependent nanotoxicity.	Size, dose	[84]
AgNPs and Ag^{+}	8.39 ± 0.98 nm by DLS.	0.03, 0.16, 0.31, 0.78, and 1.55 μg mL^{-1}	3–120 hpf	Mortality; Abnormalities; Embryo heart rate; Hatching success; ROS detection; Glutathione levels; Antioxidant enzyme activities.	Dissolved Ag was more toxic than AgNPs; Both forms induced mortality and delayed hatching; ↑ Abnormalities with both Ag types, especially at the high concentrations, non-depleted yolk, bent tail, malformed spine, and edema; Both forms generated ROS and reduced glutathione levels but generally did not affect antioxidant enzymes activities; Cysteine significantly blocks the adverse effects of AgNPs and Ag^{+}.	Ag ions	[66]

(*continued on next page*)

Table 1 (*continued*)

NPs	Size	Dose	Exposure period	Assay involved	Outcomes	Influential factors	Reference
AgNPs	10 and 35 nm, and its larger counterpart 600−1600 nm.	5, 50, 500, 5000, and 25,000 μg L^{-1}	From the 1−2 cell stage (1−1.5 hpf) to 48 hpf	Survival rates; Phenotypic deformities; Cell necrosis; Metallothionein gene expression by WISH; Uptake of NPs into embryos by CARS microscopy.	Dose-dependent lethality and morphological defects, occurring predominantly during the gastrula stage; Lethality: 35 nm was significantly more toxic than 10 nm AgNPs and Ag bulk; Yolk syncytial layer as a target tissue for AgNPs toxicity; No evidence of particles crossing the chorionic membrane in exposed embryos; Ag ions play a major role in the toxicity of AgNPs, and coating with citrate or fulvic acid decreased toxicity significantly; Heavy metal stress response gene metallothionein 2 increased at sub-lethal exposures.	Size, dose, Ag ions, coatings	[73]
Spherical and flat AgNPs; $AgNO_3$	Nanoplates (20−50 nm); Nanospheres (4.6−12.6 nm)	LC50: 0.0169, 0.0415, and 0.0649 mg L^{-1} for nanoplate, nanosphere, and ions.	0−96 hpf	Ecotoxicity testing (mortality, hatching embryos, and malformations)	Ag nanoplates were more harmful than Ag nanospheres. The harmful effects of AgNPs may be associated with the particles themselves than with ionic silver released into the solution.	Shape, particulate itself	[25]
Colloidal AgNPs (cAgNPs) Gold nanoparticles (cAuNPs)	3, 10, 50, and 100 nm	0.25, 2.5, 25, 100, and 250 μM	4, 24, 48, 72, 96, and 120 hpf	Determination of particle uptake; Sublethal endpoints.	cAgNPs produce almost 100% mortality at 120 hpf while cAuNPs produce less than 3% mortality; cAgNPs generate a variety of embryonic morphological malformations, while cAuNPs induce minimal sublethal toxic effects; cAgNPs toxicity is slightly size dependent at certain concentrations and time points; cAgNPs toxicity is caused by the particles themselves or Ag^{+} that is formed during *in vivo* particle destabilization; Chemistry is as, if not more, important than specific nanosizes at inducing toxicity *in vivo*.	Size, particulate, surface chemistry	[80]
Amine-modified AgNPs	10 and 50 nm	0.1, 1, and 10 μg mL^{-1}	24, 48, 72, and 120 hpf	Distribution of the AgNPs in developing embryos by AAS; Evaluation of chorion pore size; Embryo mortality and morphological abnormalities; ROS quantification and intestinal damage; Lysosomal activity and apoptosis.	AgNPs were taken up into embryos via the chorion; The larger-sized led to an enlarged chorion pore size and were distributed throughout developing zebrafish tissues to a greater extent than small-sized ones; Time-course survivorship revealed dose- and size-responsive effects; Abnormal phenotypes; Larger-sized changed lysosomal activity and increased apoptotic cells of developmental organs in the embryo.	Size, time, dose	[86]
Polypyrrolidone (PVP) or citrate surface coatings AgNPs	20 or 110 nm	0.08, 0.4, 2, 10, and 50 mg L^{-1}	From 6 to 120 hpf	Embryonic mortality; Percentage of malformation; Quantification of silver by ICP-MS; Developmental toxicity profiles.	Exposure of embryos to AgNPs suspended in ultrapure water and $CaCl_2$ resulted in higher toxicity than suspensions in embryo medium; 20-nm AgNPs were more toxic than 110-nm AgNPs; PVP coating was more toxic than the citrate coating at the same particle core size; Size- and surface-coating-dependent toxicity is a result of AgNPs remaining unagglomerated.	Size, coatings, medium milieu	[87]

Specific stages of embryos: (I) cleavage, (II) early gastrula, (III) early segmentation, (IV) late segmentation, and (V) hatching stage.
Abbreviation: Atomic Absorption Spectrophotometer (AAS); Citrate-coated AgNPs (AgNPs-C); Coherent Anti-Stokes Raman Scattering (CARS); Days post-fertilization (dpf); Dynamic Light Scattering (DLS); Hours post-fertilization (hpf); Inductively coupled plasma mass spectrometry (ICP-MS); Nanoparticles (NPs); Nanosilver/silver nanoparticles (AgNPs); Nitric Oxide (NO); Polyvinylpyrrolidone-coated AgNPs (AgNPs-PVP); Reactive oxygen species (ROS); Whole Mount In Situ Hybridization (WISH).

cause of harmful effects instead of ionic silver released from particles [25,74,75], recent studies have authenticated that free Ag^+ is not the sole contributor to embryonic developmental impairments, as no additional free ions were released but still incurred head deformities, neural hypoplasia, and cardiac defects [76]. Adverse developmental outcomes can be partially attributed to small-scale particles accumulating in the brain and disrupting neural development [76]. Furthermore, AgNPs have been found to block erythrogenesis and damage the hematopoietic process, which is dominantly explained by intriguing particles other than releasing ions [75]. Acute exposure to polyvinylpyrrolidone-coated AgNPs (AgNPs-PVP) but not Ag ionic form in early embryos has been found to incur vascular hypoplasia in later life cycles [77].

AgNPs have been mainly reported to be oxidized from Ag^0 to Ag^+ or Ag^{2+} [78]. However, recent studies have found that Ag^{3+} formation on the particle surface in existing humic acid can significantly decrease the harmful effects of AgNPs on zebrafish embryos [78]. Additionally, the leachate released from AgNPs-containing commercial products or their supernatant showed more toxicity than silver nitrate ($AgNO_3$), suggesting that other factors during manufacturing might contribute to high toxicity [79]. Collectively, the embryotoxicity and long-term defects of AgNPs can be derived from particles themselves, Ag ions, or the formation of new compounds due to the instability and destabilization of AgNPs *in vivo* [80].

2.2.3. Nano-related size properties

A cluster of studies found that smaller-sized AgNPs exhibit a more significant effect than larger ones [81,82]. This is because smaller particles have a larger surface-to-volume ratio, leading to a wider reaction area and facilitating the release of silver ions. Additionally, smaller-sized AgNPs are more likely to enter embryos through the chorionic pore, which has a 0.5–0.7 μm diameter based on optical imaging [52] and field emission–scanning electron microscopy (FE-SEM) [83]. Spherical-shaped AgNPs around tens of nanometers can passively diffuse into embryos via random Brownian motion and remain inside throughout embryonic development [84,85]. It was found that smaller AgNPs are more likely to pass through chorionic canals via Brownian diffusion or cause lethality before hatching by forming aggregates that block and inlay chorionic pores. In contrast, larger AgNPs form aggregates easily expelled by the chorionic membrane [52]. While previous research suggested that smaller AgNPs were more convenient for embryos, a recent study contradicted this finding and suggested that larger-sized AgNPs were distributed more extensively throughout developing tissues, possibly due to the enlarged pore perforation onto chorion [86]. Therefore, AgNPs can be internalized into embryos, but the size-dependent effects are unclear. However, there are conflicting reports on the distribution of AgNPs in zebrafish embryos. Some studies suggest that AgNPs are completely and uniformly distributed on the surface of the chorion without entering the embryos [57].

In addition, controversies also exist regarding the adverse outcomes of developing zebrafish. Several studies have shown that smaller-sized AgNPs can have more intense adverse effects than larger-sized particles. For example, 20-nm AgNPs were more toxic than those of 110 nm [61,87], and 12-nm AgNPs were more bioactive than those of 21 nm [88]. Additionally, 4-nm AgNPs were found to be more efficient in embryos compared to those of 10 nm [76,89], and 4 nm-treated groups showed developmental defects such as shortened body length and delayed yolk sac absorption, while 10 nm did not [89]. Contradictorily, reports suggest that larger-sized AgNPs can be more toxic than smaller particles, as seen in a study comparing 41.6 ± 9.1 nm vs. 11.6 ± 3.5 nm at an identical molar concentration [84]. A recent study also found that 50-nm AgNPs exerted more severe subcellular structure damage, apoptosis, and abnormal phenotypes than 10-nm AgNPs, possibly due to the significantly increased distribution of larger particles due to enlarged chorion pores [86].

Intriguingly, research has shown that 40-nm particles are more likely to become trapped in the intestinal lumen, leading to lethal consequences, compared to particles of 10 or 100 nm in size [74]. However, why 40-nm AgNPs are more easily taken up than larger or smaller counterparts remains unclear. In addition, studies have found that 35-nm AgNPs are significantly more toxic than smaller (10 nm) and larger (600–1600 nm) particles [73]. Furthermore, PVP-coated AgNPs at smaller sizes have been found to cause behavioral hypoactivity, while larger particles induced hyperactivity [90]. Therefore, size-dependent effects may occur at specific nanoscale dimensions, concentration intervals, and time points. Determining the threshold value of uptake, peak load capacity, and toxicological performance, particularly concerning particle size, remains ambiguous.

2.2.4. Nano-related surface properties

Surface chemistry plays a crucial role in the embryotoxicity of AgNPs. The type of coating is a key factor in controlling their biocompatibility. For example, AgNPs coated with PVP are more toxic than those coated with citrate [61,87]. However, other studies have shown that PVP-coated AgNPs do not affect embryo survival or morphology, while citrate-coated AgNPs delay hatching to a similar degree as Ag ions [90]. Peptides-functionalized AgNPs are much more biocompatible than citrate-modified AgNPs [85]. All the above information indicates that surface coating is an important factor in controlling the biocompatibility of AgNPs.

In addition to capping agents, surface charge has also been shown to play a crucial role in regulating the biological consequences of AgNPs. This is exemplified by the controllable diffusion coefficients, which rely on surface charge-dependent but size-independent electrostatic interactions with the embryonic milieu. Positively charged AgNPs have been found to diffuse faster and travel longer than their negatively charged counterparts, resulting in relatively enhanced biocompatibility due to weaker interactions with embryonic molecules. However, more negative charges have been associated with increased toxicity [85]. Overall, the surface chemistry of AgNPs is an important factor to consider when evaluating their potential embryotoxicity. Therefore, precise surface modifications to increase biocompatibility could be a promising strategy for designing AgNPs with a wide range of applications. Regarding embryonic development, the toxicity of certain NPs is more strongly influenced by surface area than the determinant of particle mass or number [88]. This highlights the importance of considering surface area and mass units or particle numbers when evaluating nanotoxicity.

2.2.5. Nano-related shape properties

A wide range of characteristics, such as chemical composition, particle size, surface chemistry, and agglomeration status, contribute to the harmful effects of AgNPs. The shape of the particles is a particularly important factor, with nanoplates being more hazardous on zebrafish (*Danio rerio*) embryos than nanospheres [25]. This shape-dependent effect has been consistently observed in *Chlorococcum infusionum*, an alga, but the shape seems a secondary influencing factor relative to the diameter of AgNPs [91]. On the contrary, other studies showed that spherical AgNPs are more bioactive than the flat shape of nanoplates. For example, nanospheres exerted better antibacterial capabilities than the shape of triangle nanoplates [92]. Ag nanospheres significantly reprogrammed cellular energy metabolism more than nanoplates in both tumor and nontumor cells. Smaller nanospheres showed greater

alteration than larger-sized spherical AgNPs [93]. Therefore, more evidence is still required to reach a compelling conclusion.

2.2.6. Other influential factors

The toxicity of AgNPs on embryonic development is also influenced by other factors, including the presence or absence of the chorion, the specific stage of developmental embryos, and the husbandry environment. For instance, developmental abnormalities were more severe in the absence of chorion [61], and embryos in the cleavage stage showed more complex abnormalities than hatching embryos [94,95]. The aqueous growing environment is a potential variable for determining embryotoxicity due to the precise regulation of dissolved Ag ions, silver speciation, particle aggregation, bioaccumulation, and bioavailability. Studies have shown that AgNPs release more Ag ions when dissolved in deionized water than a standard zebrafish embryo medium, leading to diverse biological endpoints in different milieu [57,74]. Zebrafish facility water and normal growing media have been found to cause differential developmental alterations, with the former being more toxic [78]. In addition, calcium chloride and ultrapure water have also been found to show worse hazards in embryonic development than standard zebrafish embryo medium due to the less agglomeration of AgNPs in low or no ionic-strength environments [87], highlighting the importance of considering the impact of the aqueous environment on the toxicity of AgNPs.

Understanding these factors and their complex interactions is crucial for developing appropriate measures to restrain the potential hazards of AgNPs effectively. While the embryotoxicity of AgNPs in zebrafish has been partially determined, further research is needed to refine the influencing factors.

2.3. In vitro model for embryotoxicity assessment

In vitro, studies have shown that AgNPs can significantly impact ESCs, including reduced cell viability, increased apoptosis, changes in cell morphology, and stimulating the formation of autophagosomes [96–100]. Table 2 summarizes the hazardous effects of AgNPs on embryos *in vitro,* while Fig. 2 provides mechanistic insights into these effects.

ESCs are pluripotent cells that can differentiate into different types of cells. Researchers used ESCs as an *in vitro* model to predict the embryotoxicity of chemicals and found that subcytotoxic concentrations of AgNPs inhibited cell differentiation [99]. One study reported that AgNPs affected ESCs to differentiate into hepatocytes *in vitro* by down-regulating hepatocyte markers in hepatoblasts and reducing glycogen storage during the formation phase of hepatocyte-like cells [97]. A similar failure was observed in differentiation into cardiomyocytes in response to AgNPs [97]. AgNPs also inhibited the fibroblast growth factor (FGF) signaling pathway in human-derived ESCs (hESCs) at human-relevant concentrations within 0.1 μg mL^{-1}, thereby affecting the development of cranial placodes in the absence of cytotoxicity and reactive oxygen species (ROS) [101]. Furthermore, AgNPs disordered the X chromosome-linked genes and consequently affected the differentiation of female mouse-derived ESCs (mESCs) but did not affect the differentiation of male mESCs under identical circumstances [99]. Further, females seemed more susceptible to neurodevelopmental damage than males on exposure to AgNPs [40,41].

As the dose of AgNPs increased, subcellular damage, cell morphology disruption, and cell viability changes were observed. When the concentration reached the cytotoxicity threshold, pluripotent C57BL/6 mESCs experienced a significant reduction in cell viability when exposed to 20 nm AgNPs at concentrations greater than 1 μg mL^{-1} [96]. Similarly, Sprague-Dawley (SD) rat-derived ESCs (rESCs) treated with AgNPs (<100 nm) at concentrations ranging from 2.5 to 60 μg mL^{-1} showed a dose-dependent decrease in cell viability, as well as mitochondrial damage, endoplasmic reticulum swelling, and the formation of apoptotic vesicles [102].

Several studies have demonstrated that exposure to AgNPs during embryonic development can produce neurotoxicity in offspring. In both human- and rat-derived embryonic neural stem cells (ENSCs), exposure to AgNPs with an average diameter of 23 nm led to a significant decrease in proliferation, attributed to an overproduction of ROS and lactate dehydrogenase (LDH) [98]. Additionally, a dose-dependent decrease in mitochondrial activity and an increase in apoptotic cells were observed, which can be reversed by the antioxidant acetyl L-carnitine [98]. Similar adverse effects were observed in hESCs-derived neural stem/progenitor cells exposed to AgNPs with a mean diameter of 7.9 nm, which exhibited a dose-dependent decrease in cell viability, dysfunctional neurogenesis, cell cycle arrest, and apoptosis [100]. Weldon et al. investigated the developing neurotoxicity of AgNPs in three-dimensional primary organotypic cultures and found a dose-dependent increase in cytotoxicity at later sensitive differentiation stages. Moreover, it interestingly showed that despite the lower uptake of 20-nm particles compared to those of 110 nm, *in vitro* cultures were more sensitive to smaller AgNPs at comparable dosimetric dosage levels [103]. However, although aged AgNPs were less cytotoxic than pristine AgNPs, neither induced developmental toxicity in mESCs because of the inhibition of differentiation observed at cytotoxic levels [104].

3. Adverse effects of AgNPs on fetal development

Parental exposure to AgNPs can potentially impact the health of fetuses and offspring. While much of the research has focused on maternal exposure and its effects on progeny, there is a need for further investigation into fetal health after male exposure. Exposure to harmful substances during pregnancy can lead to adverse pregnancy outcomes (APOs) [105,106], and the fetus is particularly sensitive to exogenous substances during development. Studies have shown that exposure to AgNPs can cause changes in pregnancy parameters, such as an increase in non-viable fetuses and a decrease in birth weight. Compared to the control group, pregnant CD-1 mice that were given a single dose of 10 mg kg^{-1} of AgNPs with an average size of 20 nm via gavage on GD9 showed a significant increase in non-viable fetuses, despite the absence of maternal weight loss or behavioral changes [107]. Similarly, Wistar rats orally administered with 25 mg kg^{-1} of AgNPs with a mean particle size of 20 nm per d during full gestation experienced a decrease in birth weight [45]. In another study, NMRI mice that were orally administered with 1 mg kg^{-1} d^{-1} of AgNPs with a diameter of 70 nm during different periods (GD1–7, GD8–14, or GD1–14) showed varying outcomes in fetuses, which were overseen through dissection on GD15. GD8–14 seemed to be a sensitive window of developmental hazards to the fetus, shown as decreased viable numbers, fetal weight decline, drop in crown-rump lengths, and increased malformation. There were also significant increases in necrotic and apoptotic cells and the extent of fibrosis in the midbrains of fetuses from the AgNPs group [108]. However, it is interesting to note that placental weight and circumference in the AgNPs-treated groups were comparable to those in the control, but the function and histological state of the placenta have not been reported. Further research is needed to fully understand the potential risks of AgNPs exposure during pregnancy and its effects on offspring health.

While numerous animal studies have reported APOs due to in-utero exposure to AgNPs, studies have also demonstrated no adverse effects. For instance, one study found no significant

Table 2
Hazardous Effects of AgNPs on embryos *in vitro*.

In vitro embryo	Size	Dose	Exposure period	Methods/Assay used	Outcomes	Reference
Rat embryonic cells	≤100 nm	Cytotoxicity: 2.5, 5, 10, 20, 40, and 60 μg mL^{-1}; TEM and DNA microarray: 20 μg mL^{-1}.	Cytotoxicity: 24 h; TEM: 2, 4, 24, and 48 h; DNA microarray experiment for only 48 h.	MTT; TEM; qRT-PCR; DNA microarray.	Cell viability was dose-dependently decreased; AgNPs were found in nuclei, mitochondria, cytoplasm, and lysosomes; Induced mitochondrial destruction, distension of endoplasmic reticulum, and apoptotic bodies; 23 pathways were affected with the most changes in inflammatory responses; ↑*mmp3* and ↑*mmp9*.	[102]
hESCs-derived NPCs	7.9 ± 0.95 nm	Cytotoxicity and ROS measurement, 10, 25, 50, 100, and 200 μg mL^{-1}; Cell cycle analysis, apoptotic assay: 25 and 50 μg mL^{-1}; Microarray analysis: 25 μg mL^{-1}.	6 and 24 h	Immunocytochemistry; Flow cytometry; Cell viability assay (CCK-8); LDH measurement; Apoptotic cell death assay; Intracellular ROS measurement; Microarray analysis.	No significant decrease of cell viability at 6 h, but dose-dependently decreased at 24 h; Cell rounding, detachment from the plates, and an irregular shape at 50 μg mL^{-1}; Cell cycle arrest at G1; LDH increased and reached the peak at 50 μg mL^{-1} at 24 h; AgNPs induced oxidative stress, apoptosis, and dysfunctional neurogenesis; Dynamic nature of transcriptional changes in response to AgNPs. AgNPs induce neurotoxicity through Nrf2-mediated oxidative stress and dysregulation of nervous system development.	[100]
mESCs from C57BL/6	20 nm	Cytotoxicity: 0.1 −50 μg mL^{-1}; Oxidative stress, apoptosis, and global gene expression profiling: 5 μg mL^{-1} of AgNPs and 1 or 5 μg mL^{-1} Ag^{+}.	24 h	ICP-MS; MTS assay; RNA processing and microarray experiment; Oxidative stress assay; Apoptosis by flow cytometric analysis.	In adherent culture: significant concentration-dependent cytotoxicity at concentrations >1 μg mL^{-1}, Ag^{+} appeared much more potent than AgNPs; Low concentrations of Ag^{+} (0.5 μg mL^{-1}) increased cell viability almost 20%; In embryoid body state: differentiating mESCs appeared more resistant to AgNPs and Ag^{+} than in adherent culture, with no significant cytotoxicity at Ag^{+} < 2 μg mL^{-1} or AgNPs <5 μg mL^{-1}; Embryonic development and metabolism were impacted; AgNPs induced oxidative stress and apoptosis.	[96]
Primary organotypic mouse midbrain cultures derived from C57BL/6 (GD11) and A/J mice (GD12)	AgNPs-C (20 and 110 nm); AgNPs-PVP (110 nm); All AgNPs include a 7 nm gold core.	6.25, 12.5, 25, and 50 μg mL^{-1}	24 h from DIV7, 14, and 21 to DIV8, 15, and 22	LDH assay; ICP-MS.	Significantly greater cytotoxicity at DIV15 compared to DIV8 and 22 in both C57BL/6 and A/J strains; Greater uptake of particles occurring at later time points; When assessed by dosimetric dose, more sensitive to smaller-sized AgNPs, despite less overall uptake of Ag compared to larger particles.	[103]
Female mESCs	20 nm	Screening of sublethal concentrations: 0.5, 1, 2, 4, 8, and 10 μg mL^{-1} for five days; Other: 0.2, 0.5, and 1 μg mL^{-1}.	Differentiation assays: 3 and 5 days	Cell viability: MTT, CCK-8; Cell death determination: PI staining; LDH assay; ROS generation assay; Enzyme activity assessment; Cellular localization and uptake; Western Blotting; AP staining; qRT-PCR; ChIP assay.	No observable cytotoxicity lower than 4 μg mL^{-1} for five days; Significant differentiation retardation in female ESCs, while no impaired differentiation in male ESCs; Disordered X chromosome inactivation, the X-linked genes were repressed; Deceased expression of genes is closely involved in orchestrating ESC differentiation.	[99]
hESCs	AgNPs: 20 nm; $AgNO_3$	Ectodermal differentiation: 0.001, 0.01, and 0.1 μg mL^{-1}; Cytotoxicity: 0.001, 0.01, 0.05, 0.1, and 0.5 μg mL^{-1}; Hyperspectral imaging: 1 μg mL^{-1}; ICP-MS: 0.01 and 0.1 μg mL^{-1}.	Ectodermal differentiation: full period; Cytotoxicity: days 2 and 12 of the differentiation; ROS: 2 h, 48 h, and 8 days; Hyperspectral imaging: day 12; ICP-MS: 24 h.	Ectodermal differentiation assays; Cytotoxicity assay; ROS; Immunofluorescence staining measurement; Hyperspectral imaging; qRT-PCR; ICP-MS.	AgNPs accumulated in cells and slightly affected neural ectoderm, neural crest, and non-neural ectoderm differentiations; Only cranial placode specification was significantly affected by AgNPs and $AgNO_3$ by inhibiting the FGF signaling pathway; Low concentrations (0.001−0.5 μg mL^{-1}) of AgNPs and $AgNO_3$ yielded no cytotoxicity or ROS; ↑ *pax6* and ↑ *six3* during cranial placode differentiation; No significant changes in the expression of autophagy-related genes.	[101]

(*continued on next page*)

Table 2 (*continued*)

In vitro embryo	Size	Dose	Exposure period	Methods/Assay used	Outcomes	Reference
Human Hepatocyte-like Cells and Cardiomyocytes	AgNPs: 20 nm; $AgNO_3$	Developmental toxicity: 0.001, 0.01, and 0.1 μg mL^{-1}; Cytotoxicity: 0.001, 0.01, 0.05, 0.1, and 0.5 μg mL^{-1}.	Cytotoxicity: 2 and 12 days of differentiation; Hepatic differentiation: days 0–18 of differentiation; Cardiomyocyte differentiation: full differentiation period.	DLS analyses; AlamarBlue assay; Periodic Acid-Schiff (PAS) staining; qRT-PCR; Immunofluorescence staining.	Impaired the generation and functions of hepatocytes-like cells derived from endoderm; Decreased the expression of hepatocyte marker genes *afp*, *alb*, and *hnf4a*; Altered glycogen storage; AgNPs increased while $AgNO_3$ decreased the expression of typical cardiac markers (*nkx2.5*, *myh6*, and *isl*) in HESC-derived cardiomyocytes; Mesendoderm-derived cell types, tissues, and organs may be more prone to AgNPs toxicity than ectoderm lineages.	[97]
Human ENSCs & Rat ENSCs derived from SD rats (GD16)	23 nm	1, 5, 10, and 20 μg mL^{-1}	24 h at DIV8	LDH and MTT assay; Immunocytochemistry and nuclear staining; 5-Ethynyl-2′-Deoxyuridine incorporation assay; TUNEL assay; DCF assay; 8-oxodG ELISA; Western blotting.	↓ Mitochondrial activity and ↑LDH release in a dose-dependent manner; ↑ Bax protein expression; ↑ TUNEL-positive cells and ↑ROS; ↓ ENSC proliferation; Induced cell death in rat and human ENSC models; Both apoptosis and necrosis in a dose- and duration-dependent manner; Antioxidant agent acetyl-L-carnitine effectively blocked these adverse effects.	[98]
Newborn Neurons derived from the hippocampus of SD rats (PD14)	20.67 ± 2.37 nm	2, 4, 6, 8, and 16 μg mL^{-1}; TEM analysis: 4 μg mL^{-1}	12, 24, and 72 h	Immunofluorescence; CCK-8 (for 24,72 h); WST-8; Live-dead cell staining (for 72 h); MMP detection; ICP-MS; TEM; Flow cytometry analysis; TUNEL staining; Western blotting.	AgNPs aggregated in the cytoplasm and lysosomes; The viability of neural cells began to decline at 2 μg mL^{-1}; Neurons lost their neuritic extensions and dendritic spines in a dose-dependent manner; ↓ MMP; ↑ Apoptotic cells in a concentration-dependent; ↑ SOD activity; ↑ FOXO3 while ↓ Nrf2 protein level; Induced autophagosome formation.	[123]

Abbreviation: Albumin (*alb*); Alkaline phosphatase (AP); Alpha fetoprotein (*afp*); Chromatin immunoprecipitation (ChIP); Citrate-coated AgNPs (AgNPs-C); Days *in vitro* (DIV); Dynamic light scattering (DLS); Embryonic neural stem cells (ENSCs); Fibroblast growth factor (FGF); Forkhead Box O3 (FOXO3); Hepatocyte nuclear factor 4, alpha (*hnf4a*); Human embryonic stem cells (hESCs); Hyperspectral imaging (HSI); Inductively coupled plasma mass spectrometry (ICP-MS); ISL LIM homeobox (*isl*); Lactate dehydrogenase (LDH); Matrix metallopeptidase 3 (*mmp3*); Matrix metalloproteinase 9 (*mmp9*); Mitochondrial membrane potential (MMP); Mouse Embryonic Stem Cells (mESCs); Myosin, heavy chain 6, cardiac muscle, alpha (*myh6*); Neural stem/progenitor cells (NPCs); NFE2 like BZIP transcription factor 2 (NRF2); NK2 homeobox 5 (*nkx2.5*); Paired box 6 (*pax6*); Polymerase chain reaction (PCR); Polyvinylpyrrolidone-coated AgNPs (AgNPs-PVP); Propidium iodide (PI); Reactive oxygen species (ROS); SIX homeobox 3 (*six3*); Superoxide dismutase (SOD); Transmission electron microscopy (TEM); 2′7′ -dichlorofluorescin (DCF); TdT-mediated dUTP nick end labeling (TUNEL); 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-Htetrazolium bromide (MTT); 8-oxo-7-hydrodeoxyguanosine (8-oxodG).

changes in pregnancy outcomes, embryo-fetal development, or offspring growth when low concentrations (1, 3, and 5 μg kg^{-1} d^{-1}) of AgNPs were analyzed from the beginning of gestation to delivery in Wistar rats [43]. Similarly, SD rats orally administrated with AgNPs (average hydrodynamic radius at 55 nm) of different doses 0.2, 2, and 20 mg kg^{-1} d^{-1} from GD7 to GD20 showed no significant differences in birth weight or litter size, despite the presence of Ag deposits in the placenta and fetal organs (kidneys, lungs, and liver) [109]. In another study, SD rats were orally administered AgNPs with an average diameter of 6.45 nm from GD6 to GD19. Even at a high dosage of 1000 mg kg^{-1} d^{-1}, no abnormalities were found in placental or fetal weights or sex ratios between the treatment and control groups [49]. Similarly, CD-1 mice exposed to 20 nm AgNPs at concentrations of 100 and 1000 mg kg^{-1} on GD9 showed no signs of maternal injury or adverse effects on fetus survival [107]. Interestingly, the same experiment revealed that 10 mg kg^{-1} posed a hazard to the fetus [107]. This could be attributed to the greater aggregation of AgNPs at higher doses via oral administration, which impedes particle absorption by the intestines.

In addition to gastrointestinal tract exposure, AgNPs can enter the body through inhalation and systemic exposure. In C57BL/6J mice, a significant increase in embryo resorption rate and a significant decrease in the number of viable fetuses and fetal weight were observed in response to AgNPs (average diameter 10.4 nm) via non-surgical intratracheal instillation on GD2.5, GD9.5, and GD16.5 [46]. Similarly, Kunming mice administrated with AgNPs (average diameter 11.61 nm) via tail vein injection showed a significant increase in resorption rate and a dramatic decrease in fetal weight [51]. Table 3 summarizes the APOs in response to AgNPs. Although the oral route is the most studied pathway for the developmental toxicity of AgNPs, the results are not always consistent. Furthermore, other exposure pathways have been scarcely studied. Therefore, it can only be assumed that AgNPs exert harmful effects on embryos and fetuses to some extent via different exposure routes. Still, more detailed studies are required to obtain conclusive evidence.

4. Long-term hazardous effects after birth

AgNPs can be taken up and cross the placenta in *ex vivo* placental perfusion and transport models [104,110], indicating potential risks in placental impairment, embryotoxicity, and APOs. Moreover, increasing research focused on the health effects of prenatal AgNPs exposure on offspring [111]. *In vivo* detection of AgNPs in the liver, kidneys, lungs, and brain of neonates confirms the transferability of AgNPs from dams to offspring [46,107,112].

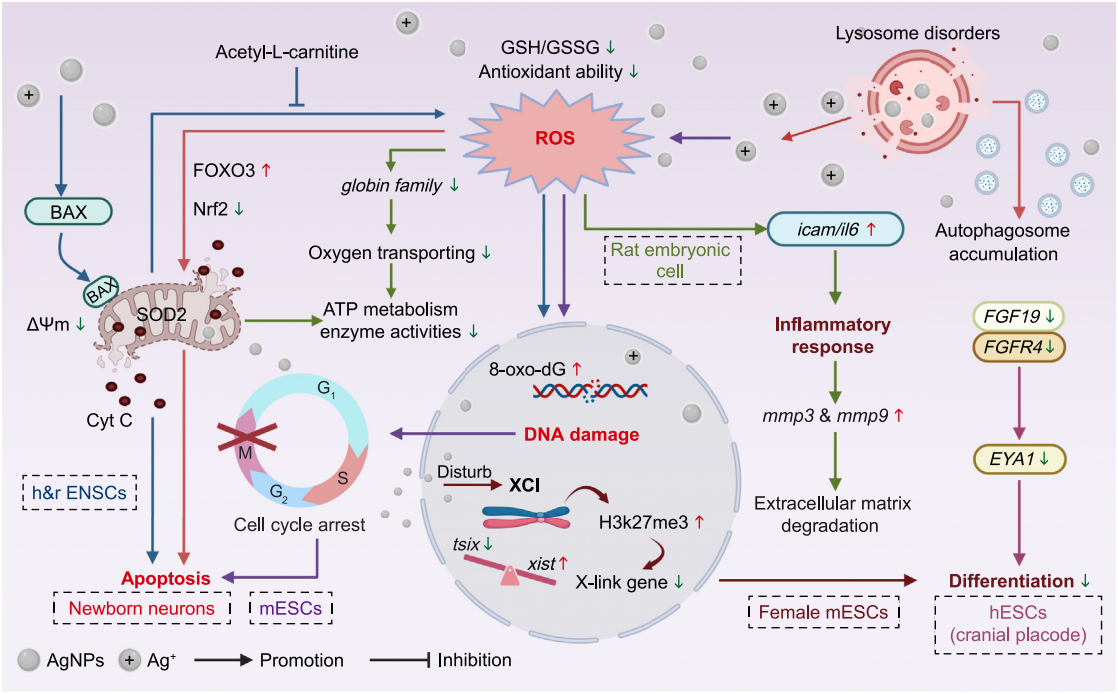

Fig. 2. Modes of action pertaining to the hazardous effects of AgNPs in *vitro* embryonic stem cell models. Abbreviations: Adenosine triphosphate (ATP); BCL2−associated X protein (BAX); Cytochrome C (Cyt C); Embryonic stem cells (ESCs); Eyes absent homolog 1 (*EYA1*); Fibroblast growth factor receptor 4 (*FGFR4*); Fibroblast growth factor 19 (*FGF19*); Forkhead Box O3 (FOXO3); Glutathione (GSH); Histone 3 lysine 27 trimethylation (H3K27me3); Human and Rat embryonic neural stem cells (h&r ENSCs); Human embryonic stem cells (hESCs); Intercellular adhesion molecule (*icam*); Interleukin-6 (*il6*); Lipid peroxidation (LPO); Matrix metallopeptidase 3 (*mmp3*); Matrix metalloproteinase 9 (*mmp9*); Mitochondrial membrane potential (MMP; ΔΨm); Mouse embryonic stem cells (mESCs); NFE2 like BZIP transcription factor 2 (NRF2); Reactive oxygen species (ROS); Superoxide dismutase [Mn], mitochondrial (MnSOD, SOD2); TSIX Transcript, XIST Antisense RNA (*Tsix*); X chromosome inactivation (XCI); X Inactive Specific Transcript (*Xist*); 8-oxo-7-hydrodeoxyguanosine (8-oxodG). Letters in uppercase with non-italic type dictate proteins. Italic uppercase letters declare genes in humans, whereas italic lower-case letters represent rodent genes. Symbols: ↓ denotes decrease; ↑ represents increase; → suggests promotion; ⊥ means inhibition.

Table 3
Adverse pregnancy outcomes in response to AgNPs.

Animal model	Exposure route	AgNPs characteristics	Dose	Exposure period	Outcomes	Reference
SD rats	Gavage	AgNPs: 6.45 ± 2.55 nm	100, 300, and 1000 mg kg^{-1}	GD6−19	No differences in gestation index, fetal deaths, fetal and placental weights, or sex ratio.	[49]
SD rats	Gavage	Citrate-capped AgNPs: 7.9 ± 0.95 nm	62.5, 125, and 250 mg kg^{-1}	Two weeks before mating, during the mating and gestation period, or/ and during four days of lactation	No significant differences in the number of living and dead pups, percentage of living and dead pups to implantations, pre-implantation loss, post-implantation loss, sex ratio, survival rate, the number of neonates with external anomalies, or body weights of pups on PD0 and PD4.	[166]
SD rats	Gavage	AgNPs: 55 nm	0.2 −20 mg kg^{-1}	GD7−20	No significant variations in pregnancy length, the number of implantation sites or resorptions, litter size, sex distribution, or offspring weights.	[109]
Wistar rats	Gavage	AgNPs: range: 2 −20 nm	1, 3, and 5 μg kg^{-1}	GD0−18	No significant differences in gestation length, litter size at birth, number of stillborn pups, or dead pups.	[43]
Wistar rats	Subcutaneous injection	AgNPs: 16 ± 4.6 nm	0.2 and 2 mg kg^{-1}	GD1, 4, 7, 10, 13, 16, and 19	No significant differences in birth weight or post-natal survival rate.	[40]
Wistar rats	Gavage	AgNPs: 20 ± 4 nm	25 mg kg^{-1}	GD1−19	↓ Birth weight of the fetus.	[45]
CD-1 mice	Gavage	AgNPs: 35.3 ± 5.8 nm	100 or 1000 mg kg^{-1}	GD9−19	↑ Mortality of fetal mice.	[107]
C57BL6/J	Non-surgical intratracheal instillation	AgNPs: 10.4 ± 0.1 nm	100 μg $week^{-1}$ with a total of 300 μg	GD2.5, 9.5, and 16.5	↑ Embryo resorption rates. ↓ Living fetuses per litter and fetal weight.	[46]
C57BL/6	Nose-only inhalation	AgNPs: 19.3 ± 2.3 nm	640 μg m^{-3}	1 or 4 h per d during GD0−10	↑ Number of resorbed embryos.	[50]
Kunming mice	Tail vein injection	AgNPs: 11.61 ± 3.38 nm	1 mg kg^{-1}	GD3.5−9.5	↑ Embryo absorption rate. ↓ The average weight of the fetus.	[51]
NMRI mice	Gavage	AgNPs: 70 nm	1 mg kg^{-1}	GD1−7, 8−14, or 1−14	↓ Weight and crown-rump length of the fetus.	[108]

Abbreviation: Gestational day (GD); Post-delivery day (PD); Sprague-Dawley (SD).

According to existing research, AgNPs exposure during fetal development can cause multiple health issues in offspring, including neurotoxicity, reproductive dysfunction, pulmonary damage, hepato-renal impairments, and metabolic disorders. The long-term adverse effects of AgNPs on offspring are summarized in Table 4 and illustrated in Fig. 3, along with the potential mechanisms depicted in Fig. 4.

4.1. Neurotoxicity in offspring

AgNPs are predicted to persist longer in the brain and testes than in other organs, which increases their sequestration in these tissues and may cause pathological damage over time [113]. AgNPs can enhance the permeability of microvascular endothelial cells and cross the blood-brain barrier [114–116], particularly during the immature period due to intrauterine exposure. Growth-associated protein-43 (GAP-43) is important for growth and plasticity as a crucial component of axon and synaptic precursors [117,118]. Maternal exposure to uncoated and PVP-coated AgNPs has been reported to disrupt synaptic plasticity by down-regulating GAP-43, resulting in detrimental effects on the spatial cognitive abilities of offspring [42].

Dopamine is an endogenous catecholamine distributed widely in both neural and non-neural tissues and plays a vital role in normal movement, learning, memory, cognition, and emotions [119,120]. Tyrosine hydroxylase (TH) is an enzyme that converts L-tyrosine to 3,4-dihydroxy phenylalanine (L-DOPA) and plays a critical role in dopamine biosynthesis [121]. Monoamine oxidase A (MAO-A) is a catabolic enzyme in dopaminergic neurons essential for dopamine catabolism and 3,4-dihydroxy phenylacetic acid (DHPA) production [122]. Studies reveal that exposing pregnant Wistar rats to 16 nm AgNPs subcutaneously at doses of 0.2 and 2 mg kg^{-1} once every three days from GD1 to GD19 can increase the levels of *mao-a* and *th* in the brains of offspring. The gene expression of *th* increased even more than the *mao-a* level, resulting in an imbalance between dopamine synthesis and catabolism [40]. Notably, female offspring showed higher sensitivity than male pups, indicating sex differences in the neurobehavioral hazards of AgNPs [40]. Research has also reported that prenatal exposure to AgNPs can cause neurodevelopmental deficits, impaired spatial cognition, and increased stress in novel environments, which are more severe in female offspring [41]. Therefore, sex plays a significant role in the developmental neurotoxicity of AgNPs following maternal exposure. AgNPs can cause redox disequilibrium and mitochondrial malfunction in a dose-dependent manner, resulting in a loss of neurite extension and dendritic spines in newborn neurons [123]. From a subcellular perspective, intracellular aggregation of AgNPs and autophagic vesicles have been observed [123], further emphasizing the crucial role of subcellular equilibrium in filial neurocyte health.

4.2. Reproductive damage in offspring

Several studies have examined the reproductive toxicity of AgNPs in offspring. Oral exposure to low doses of AgNPs during pregnancy delayed vaginal opening and testicular descent [43]. Another study found that maternal intraperitoneal injection of AgNPs during gestation caused ultrastructural changes in testicular tissues of offspring, such as detachment of Sertoli cells from the basement membrane and a loss of cohesion of germinated cells in various developmental states [44].

Moreover, AgNPs have been shown to cause membrane rupture and jeopardize intracellular components in different types of cells, such as Sertoli cells and testicular mesenchymal cells [44]. Subcellular structural analyses have indicated that delayed sexual maturation and changes in testicular ultrastructure are the main vicious events of AgNPs on the reproductive system of offspring [43,44]. Exposure of female BALB/c mice to AgNPs via intraperitoneal injection three times a week for a continuous three weeks showed developmental disturbance in pubertal mammary glands, suggesting that AgNPs may act as an emerging endocrine-disruptor by disrupting internal estrogen/estrogen receptor signal transduction [124].

4.3. Cardiopulmonary damage to offspring

There is a relative lack of studies on the pulmonary and cardiovascular damage caused by AgNPs in offspring compared to the research on neurotoxicity and reproductive toxicity. One study conducted non-surgical intratracheal instillation of AgNPs during pregnancy and found significant decreases in matrix metalloprotein-9 along with vascular endothelial growth factor-α in fetal lungs and a significant decline in fibroblast growth factor-18 at the alveolarization stage (post-delivery day PD14.5). The study also observed abnormal lung morphometry on both PD14.5 and PD49.5, indicating developmental pulmonary lesions [46].

Regarding the cardiovascular system, a study on SD rats found that a single dose of 700 μg kg^{-1} via the tail vein during the late stage of pregnancy resulted in abnormal vascular contractility/relaxation, particularly for the aortic and uterine vessels, which potentially contributed to low birth weight in newborns [125]. It is important to note that nano-related parameters, such as surface coating and size, are two pivotal factors influencing vascular health in dams and may lead to detrimental outcomes during pregnancy [125]. Specifically, citrate-stabilized AgNPs were found to disrupt vascular tissue health in the maternal uterus more severely than PVP-stabilized AgNPs [125]. Size-dependent endpoints were also evident in regulating vascular bed sensitivity, with 20 nm AgNPs-PVP demonstrating relatively lower maximum stress generation of uterine artery than the larger size of 110 nm under the same formulation of agonists [125]. These significant alterations in maternal vascular tone potentially influence fetal blood supply and resultantly enhance susceptibility to fetal growth restriction [125]. Although there is currently a paucity of direct evidence of cardiovascular hazards in offspring, the potential cardiopulmonary risks of AgNPs exposed before or/and during pregnancy should be further strengthened.

4.4. Hepatotoxicity and kidney damage to offspring

Regarding the hepatic checkpoint, a study tracked histopathological changes in the livers of neonates after oral exposure to 25 mg kg^{-1} d^{-1} of AgNPs (diameter 20 nm) from GD1–19. Dilated sinusoids and a vacuolated appearance of the hepatic tissues were observed [45]. Perinatal administration of AgNPs to female Swiss albino mice significantly caused pancreatic and renal impairments in female offspring. Proinflammatory and immune responses, metabolic reprogramming, and impaired glucose homeostasis and assimilation suffice to persist later in life up to PD150, which all pose risks of pathological changes in offspring, especially to the β-cell, proximal/distal convoluted tubular, and glomerular regions [47].

4.5. Immune and metabolic disturbance to offspring

Oral gavage of AgNPs during GD5–21 triggered systemic inflammation in dams at low dosage levels of 0.5 ppm (0.5 mg L^{-1}; 0.5 mg per kg body weight per d). However, improved anti-inflammatory immunity in fetuses persisted to later life after birth via immunological reprogramming. This suggests that a

Table 4
Long-term adverse effects of AgNPs on offspring.

Developmental hazards	Animal model	Material and size	Dose	Exposure duration	Exposure route	Observation	Adverse responses or toxicity in offspring	Reference
Neurotoxicity	SD rats	AgNPs and AgNPs-PVP: 20–50 nm; Silver nitrate and Sodium nitrate	AgNPs and AgNPs-PVP: 20 mg mL^{-1}; Ag^{+}: 2 mg mL^{-1}; Uncoated AgNPs (0.427 mg Ag per g rat), AgNPs-PVP (0.407 mg Ag per g rat), $AgNO_3$ (0.013 mg Ag^{+} and 0.007 mg NO_3^{-} per g rat), $NaNO_3$ (0.007 mg NO_3^{-} per g rat)	AgNPs and AgNPs-PVP: Every two days during GD10–18 (five times, 1 mL $time^{-1}$); Ag^{+}: GD10, 12, and 16 (3 times, 1 mL $time^{-1}$).	Intraperitoneal injection	PD35	Impaired spatial cognition in the uncoated AgNPs group; ↓*gap*-43 mRNA and protein in all treatment groups; The detected silver content in the hippocampus.	[42]
Neurotoxicity	Wistar rats	AgNPs: 16 ± 4.6 nm	0.2 and 2 mg kg^{-1}	GD1, 4, 7, 10, 13, 16, and 19	Subcutaneously injected	PD1, 7, 14, and 21	Increased gene expression of *th* and *mao-a* involved in dopamine metabolism in the brain of offspring; Female pups showed higher sensitivity than male pups.	[40]
Neurotoxicity	NMRI mice	AgNPs: 32 ± 6.6 nm	0.2 and 2 mg kg^{-1}	GD3–18	Subcutaneously injected	PD45–49	Damaged spatial cognition; Increased stress in a novel environment; Female offspring are more susceptible.	[41]
Reproductive toxicity	Wistar rats	AgNPs: Range: 2–20 nm	1, 3, and 5 μg kg^{-1}	GD0–18	Oral gavage	PD23	A delay in time for vaginal opening and testes descent.	[43]
Reproductive toxicity	Wistar rats	Green synthesized AgNPs: 17 nm	0.8 and 1.5 mg kg^{-1}	GD3–14	Intraperitoneally	At six weeks after birth	AgNPs crossed the placental and testicular barriers; Ultrastructural changes of Sertoli cells, numerous vacuoles, and cytoplasmic changes suggest the cell evolution towards necrosis.	[44]
Pulmonary toxicity	C57BL/6J mice	AgNPs: 10.4 ± 0.1 nm	100 μg $week^{-1}$ with a total of 300 μg	GD2.5, 9.5, and 16.5	Non-surgical intratracheal instillation	PD14.5 and 49.5	↓ *fgf-18* and ↓ *mmp9* at the alveolarization stage (PD14.5); ↓ VEGF protein in pup lungs at PD14.5; ↑ Mean linear intercept; ↓ Radial alveolar count; Significant increases in the mean linear intercept (MLI) and decreases in the radial alveolar count (RAC) and lung alveolar surface at PD14.5 and 49.5.	[46]
Hepatotoxicity	Wistar rats	AgNPs: 20 ± 4 nm	25 mg kg^{-1}	GD1–19	Oral gavage	PD0	↓ GPx activity; ↓ GSH level; ↑ MDA; ↑ Caspase 9 level; Fatty degeneration and congested dilated sinusoids in the liver of offspring.	[45]
Cardiovascular toxicity	SD rats	PVP or Citrate stabilized AgNPs 20 or 110 nm	A single dose of 700 μg kg^{-1}	GD17–19 (Single) Acute intravenous exposure to AgNPs during late stages of pregnancy	Intravenous administration via the tail vein	PD0	↑ Vascular tissue contractility in dams; AgNPs-PVP caused an increased force of contraction in the uterine artery and increased relaxation responses in the aorta; Citrate-stabilized AgNPs increased contractile force in both uterine and aortic vessels in dams; Alterations in fetal growth.	[125]
Immune and metabolic disturbance	Swiss albino mice	AgNPs Sigma Aldrich (Catalog number 576832)	0.5 and 2 ppm (mg L^{-1}; mg per kg body weight per d)	Gestational AgNPs exposure on pregnant mice: GD5–21 (till delivery).	Oral gavage	GD18, offspring assessed at PD2, 28, 90 days, and 10 months, 12 months	Low-dose gestational exposure to AgNPs (0.5 mg per kg body weight per d) can reprogram offspring's immunity, the effects of which persist until late adulthood, exhibiting enduring enhanced protective immune responses toward external stresses.	[48]

(*continued on next page*)

Table 4 (*continued*)

Developmental hazards	Animal model	Material and size	Dose	Exposure duration	Exposure route	Observation	Adverse responses or toxicity in offspring	Reference
Immune and metabolic disturbance, pancreatic and renal damage	Swiss albino mice	AgNPs Sigma Aldrich (Catalog number 576832)	0.5, 5, and 50 ppm (mg L^{-1})	15 days before mating and during pregnancy, the offspring were separated from the mother at PD28.	Oral gavage	PD28 and PD150	AgNPs suffice to induce significant proinflammatory and immune responses in offspring, cause metabolic reprogramming, and impair glucose homeostasis and glucose assimilation, all of which are risks of pancreatic and renal damage to offspring later in life, especially to β-cell, tubular, and glomerular regions.	[47]

Abbreviation: Fibroblast growth factor-18 (*fgf-18*); Gestational day (GD); Glutathione (GSH); Glutathione Peroxidase (GPx); Growth associated protein-43 (*gap-43*); Malondialdehyde (MDA); Matrix metalloprotein 9 (*mmp9*); Monoamine oxidase A (*mao-a*); Nanosilver/silver nanoparticles (AgNPs); Polyvinylpyrrolidone-coated AgNPs (AgNPs-PVP); Post-delivery day (PD); Sprague-Dawley (SD); Tyrosine hydroxylase (*th*); Vascular endothelial growth factor (VEGF).

relatively low level of AgNPs significantly enhances the filial immunological and metabolic capacity despite maternal systemic inflammation [48]. Intrauterine exposure to low-dose AgNPs also ameliorated streptozotocin-triggered diabetes mellitus and kidney diseases in offspring [48]. It should be noted that this study only incorporated female objectives [48], and further efforts are required to evaluate immune reprogramming in male offspring until their later life stage.

However, alterations in glucose homeostasis and assimilation, coupled with pancreatic and kidney impairments, were tracked in offspring when the concentration was increased to 50 ppm (mg L^{-1}) by perinatal exposure [47]. The immune responses and memory were disturbed by prenatal exposure to AgNPs until weaning on the maternal side [47]. Additionally, metabolic profiles were also impacted in offspring that can persist until adulthood even without additional filial exposure to AgNPs, which may provide clues for pancreatic and renal pathology later in life [47]. These findings highlight the crucial role of the concentration of AgNPs in orchestrating specific performance of immunological and metabolic reprogramming. Additionally, molecular insights into immune and metabolic alterations and the implications of modulating disease progression should be thoroughly explored.

Likewise, in the chicken embryo system, administration of AgNPs *in ovo* enhanced immunocompetence without any harmful effects on embryonic growth, suggesting AgNPs could positively modify immunity during chicken development [126]. However, the parameters or characteristics responsible for improving innate and adaptive immunity remain unclear because a fixed concentration of a certain hydrocolloid AgNPs can hardly represent all possible scenarios. Further studies are needed to strengthen our understanding of the developmental immunological and metabolic disturbance of AgNPs.

5. Potential hallmarks of developmental hazards of AgNPs

Although many *in vivo* and *in vitro* studies have been conducted on the developmental damage caused by AgNPs, there is still inadequate research to draw definitive conclusions about the molecular mechanisms involved. Currently, the lack of clear hallmarks and mechanistic insights fuels an expectation for future research

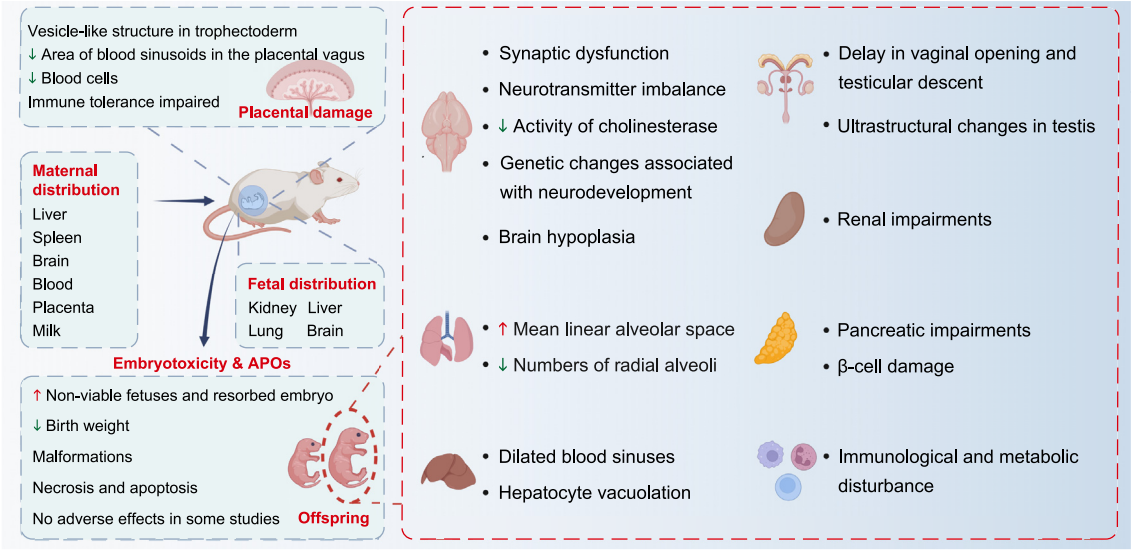

Fig. 3. Developmental impairments of AgNPs in rodent models. AgNPs cause embryotoxicity, APOs, and offspring damage in mammal rodents (mice and rats). Maternal exposure to AgNPs gives birth to placental impairments, increased embryo resorption, and perennial lesions in offspring. Longstanding deleterious outcomes involve neurodevelopmental damage, hepatorenal pathology, immune and metabolic disturbance, and pulmonary dysfunction. Abbreviations: adverse pregnancy outcomes (APOs). Symbols: ↓ denotes decrease; ↑ represents increase.

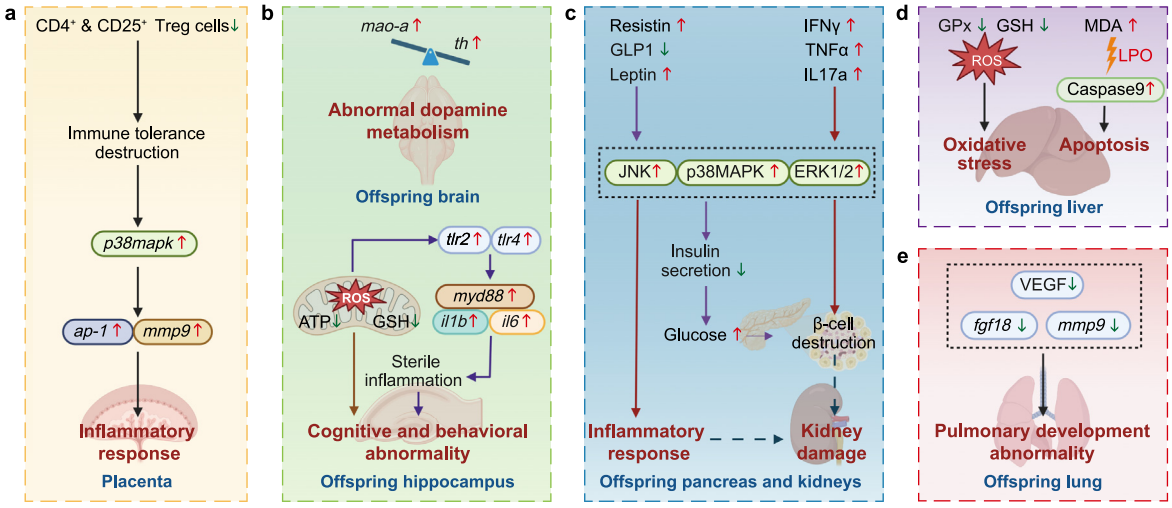

Fig. 4. Potential mechanisms of developmental hazards of AgNPs in mammal rodent models. **a**, AgNPs significantly decrease the proportion of $CD4^{+}CD25^{+}$ Treg cells and disturb immune tolerance, which causes placental inflammation via the *p38*/*ap-1*/*mmp9* signal transduction. **b**, Maternal exposure to AgNPs triggers neurodevelopmental toxicity in the offspring, characterized by behavioral and cognitive dysfunction in which abnormal dopamine metabolism and sterile inflammation are probably involved. **c**, AgNPs damage the pancreas and kidneys in offspring, evidenced by decreased insulin bioavailability and increased glucose, which are mediated by MAPK signaling pathways. **d**, Involvement of oxidative stress and apoptosis in hepatic lesions in offspring. **e**, Decreases in VEGF, *fgf18*, and *mmp9* are possibly responsible for abnormal lung development.
Abbreviations: Activator protein 1 (*ap-1*); Adenosine triphosphate (ATP); c-Jun N-terminal kinase (JNK); Extracellular signal-regulated kinase (ERK); Fibroblast growth factor 18 (*fgf18*); Glucagon-like peptide 1 (GLP1); Glutathione (GSH); Glutathione peroxidase (GPx); Interferon-gamma (IFNγ); Interleukin-1 beta (*il1b*); Interleukin-6 (*il6*); Interleukin-17a (IL17a); Lipid peroxidation (LPO); Malondialdehyde (MDA); Matrix metalloprotein 9 (*mmp9*); Monoamine oxidase A (*mao-a*); Myeloid differentiation primary response gene 88 (*myd88*); p38 Mitogen-activated protein kinase (p38MAPK); Reactive oxygen species (ROS); Silver nanoparticle (AgNPs); Toll-like receptor 2 (*tlr2*); Toll-like receptor 4 (*tlr4*); Tumor necrosis factor-alpha (TNFα); Tyrosine hydroxylase (*th*); Vascular endothelial growth factor (VEGF). Letters in uppercase with non-italic type dictate proteins. Italic uppercase letters declare genes in humans, whereas italic lower-case letters represent rodent genes. Symbols: ↓ denotes decrease; ↑ represents increase.

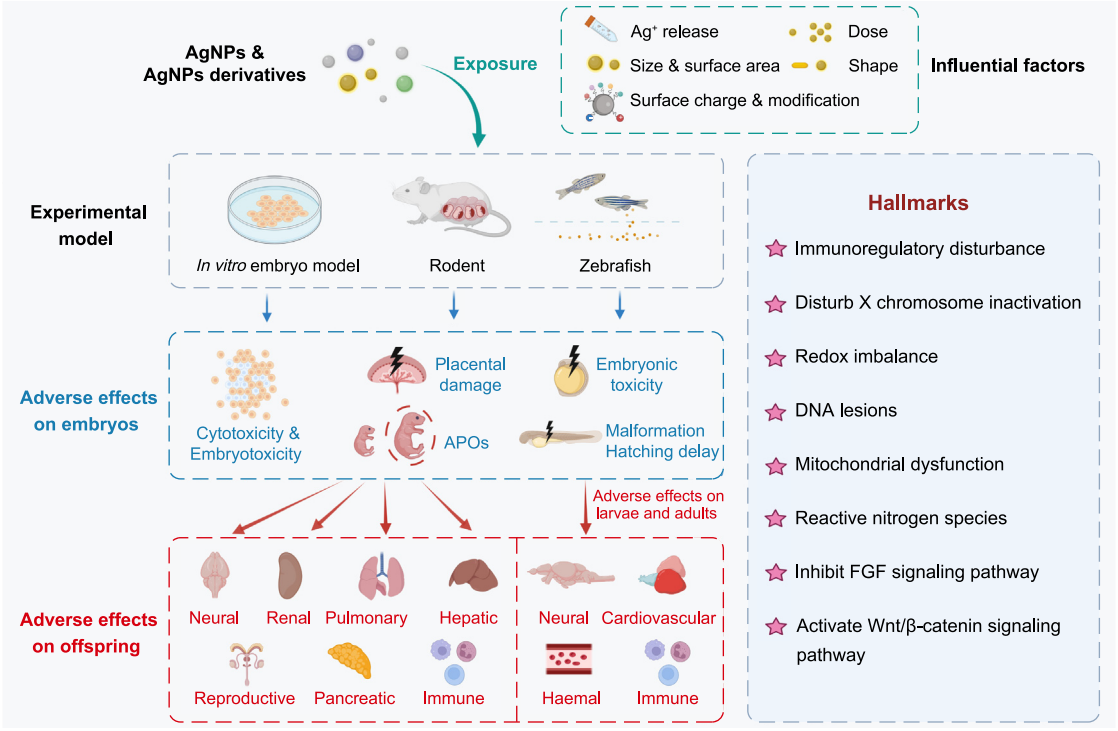

Fig. 5. Schematic graph of the developmental toxicity induced by AgNPs. In an *in vitro* embryo model, AgNPs and Ag^{+} resulted in cytotoxicity and embryotoxicity, such as induction of cell death and inhibition of cell differentiation. In the zebrafish model, AgNPs or Ag^{+} solutions resulted in embryotoxicity, such as malformations, delayed hatching, and survival reduction. The abnormal phenotypes include small heads, eye abnormality, yolk sac edema, and tail/spinal cord flexure. Long-term defects have adverse neural impacts, cardiovascular damage, haemal dysregulation, and immunological disturbance. In the rodent model, AgNPs exposure during pregnancy resulted in placental damage and APOs and even caused adverse effects in offspring. The main hallmarks of developmental hazards of AgNPs and their underlying influential factors are listed. Abbreviations: Adverse pregnancy outcomes (APOs); Fibroblast growth factor (FGF); Silver ions (Ag^{+}); Silver nanoparticles (AgNPs).

that can provide a comprehensive understanding of the underlying developmental hazards and toxicological properties of AgNPs. This will help us better regulate the hazardous aftermath during exploratory applications and allow us to tailor nano-engineered parameters to ensure the biocompatibility of newly formed AgNPs. The probable hallmarks of the developmental hazards of AgNPs are discussed in the following section, and a schematic graph is depicted in Fig. 5.

5.1. Redox imbalance

Oxidative imbalance refers to the state of stress between the production of ROS and antioxidant defenses, which can result in lipid peroxidation and even cell death [127–129]. Maintaining redox balance is crucially dependent on antioxidant capacities, such as catalase, thioredoxin, non-enzymatic systems, glutathione (GSH), vitamin C, and vitamin E, which help to respond to stresses [130–133]. Although organisms are typically resistant to oxidative stress to a certain extent, when the threshold of an alarming situation is exceeded according to the tertiary layer of oxidative-reduction proposal, AgNPs can trigger developmental adversity by igniting redox imbalance [44,45,63,64,98].

Oxidative stress is one of the primary hallmarks of AgNPs toxicity [134]. The dissolution of metal NPs increases free radicals that can cause oxidative damage [135,136]. Embryos and newborns are particularly vulnerable to oxidative stress due to their high metabolic rates [137]. Glucose-6-phosphate dehydrogenase (G6PDH) is known to resist oxidative damage caused by high levels of ROS when overexpressed [138]. In catfish embryos exposed to AgNPs, a decrease in total antioxidant capacity was observed, as evidenced by significant decreases in G6PDH and catalase [64]. Additionally, malondialdehyde (MDA) levels were significantly increased in AgNPs-treated medaka (*Oryzias latipes*) embryos, indicating that AgNPs may induce embryotoxicity through lipid peroxidation [63]. Therefore, oxidative stress plays a crucial role in the destructive responses triggered by AgNPs in embryos.

Oxidative stress caused by AgNPs can result in persistent tissue damage in offspring even after birth. Bidian et al. observed significant changes in MDA and GSH/oxidized glutathione disulfide (GSSG) ratio in the testicular tissues or offspring serum, indicating prolonged lipid peroxidation and oxidative damage after birth [44]. Similarly, decreases in glutathione peroxidase (GPx) and GSH, along with an increase in MDA in the liver of offspring, emphasized the importance of redox disequilibrium as a hallmark of developmental damage caused by AgNPs [45].

The mechanisms of developmental toxicity associated with AgNPs are complex and diverse, extending beyond the oxidative stress described above. Researchers have proposed additional modes of action, such as reactive nitrogen species (RNS) and nitrative stress. High levels of ROS/RNS can lead to cellular damage, including necrosis and apoptosis [139]. The exposure of embryonic zebrafish to AgNPs resulted in a significant rise in intestinal nitric oxide level, suggesting the induction of RNS and nitrative stress [74].

5.2. Immunoregulatory disturbance

The immune system protects the body by recognizing “self” and “non-self” components. During mammalian pregnancy, the body undergoes a state of immune tolerance essential for successful placenta formation and maintenance of pregnancy [140]. The maternal immune system can tolerate the embryo/fetus to sustain a successful pregnancy [141,142]. However, exposure to AgNPs during pregnancy can significantly reduce the number of $CD4^+$ and $CD25^+$ natural regulatory T cells [51], which play an important role in maternal immunity and tolerate foreign antigens in the fetus [143]. This impaired maternal immune tolerance can trigger an inflammatory response with elevated expression of interleukin-6 and interferon-γ in the placenta via activating the *p38mapk/ap-1/mmp9* pathway [51]. Additionally, studies by Campagnolo et al. have observed a placental inflammatory response mediated by tumor necrosis factor-α and interleukin-1β in response to AgNPs [50].

5.3. DNA lesions

The role of DNA in the transmission of genetic information is well known, and studies have confirmed that AgNPs with diameters less than 10 nm can diffuse into the nucleus through multiple nuclear pores (the effective size of 9–10 nm for nuclear pores) and directly damage genetic materials [144,145]. The phosphorylation of H_2AX (γ-H_2AX) is a biomarker of DNA damage and one of the initial stages of DNA double-stranded breakage [146,147]. Studies have reported that elevated levels of γ-H_2AX in developing embryos, which supports the notion that prenatal exposure to AgNPs can cause substantial DNA lesions [148]. In addition, AgNPs increase DNA deletions in developing embryos, cause irreversible chromosomal damage in bone marrow, and induce DNA lesions in peripheral blood or bone marrow [148]. Furthermore, AgNPs increase the level of 8-oxo-7,8-dihydroguanine/7,8-dihydro-8-oxoguanine (8-oxoG) due to substantial oxidation, which is more severe in the *MutY homolog* (*myh*) knockout mice [148], as *myh* encodes a DNA glycosylase involved in oxidative DNA repair, and the significant incapacitation of base excision repair may be responsible for permanent genome instability under AgNPs stimuli.

Proliferating cell nuclear antigen (PCNA) plays a vital role in DNA replication and repair [149]. Abnormal elevation in PCNA levels was observed in zebrafish after embryonic exposure to AgNPs, partially indicating DNA damage [150]. Similarly, AgNPs caused large amounts of DNA breakage in catfish embryos [64]. *In vitro* observation also supports this phenomenon, as AgNPs elevated 8-oxo-7-hydrodeoxyguanosine (8-oxodG) levels in ENSCs, which indicated oxidative DNA damage [98]. Furthermore, AgNPs significantly downregulate most base excision repair-related genes, disrupting DNA damage repair and enhancing the susceptibility to genome instability, which may be an important mechanism of vicious DNA damage caused by AgNPs [98].

5.4. Subcellular dysfunction

Mitochondria are the main sites for energy production in cells, and they have multiple interrelated functions, including adenosine triphosphate (ATP) synthesis and biosynthetic intermediates [151–153]. They also contribute to cellular stress responses such as mitochondrial superoxide anions, autophagy, and apoptosis [128,129,152,154,155]. The superoxide dismutase (SOD) family of enzymes plays a crucial role in maintaining cellular homeostasis, with SOD1 localized in the cytoplasm; superoxide dismutase [Mn], mitochondrial (MnSOD, SOD2), localized in the mitochondrial matrix; and SOD3 located extracellularly [156]. SOD catalyzes superoxide into hydrogen peroxide (H_2O_2), which is then decomposed by catalase into hydrogen and water for the dynamic maintenance of cellular redox balance [157]. AgNPs have been shown to impair newborn neurons through redox imbalance, as indicated by a significant increase in cellular SOD enzyme activity and collapse of mitochondrial membrane potential [123]. After receiving apoptotic signals, BCL2-associated X protein (BAX) translocates from the cytosol to the surface of mitochondria, leading to increased membrane permeability, decreased membrane potential, and eventual apoptosis [158]. Upregulation of BAX was detected in human and rat ENSCs after AgNPs exposure,

accompanied by the transfer of BAX to mitochondria from the cytosol. In addition to mitochondrial oxidative damage, AgNPs slow or even halt cell proliferation [98], with most deposition tracked inside the nucleus, which caused genetic materials damage and cell apoptosis, responsible for further developmental retardance [159].

5.5. Signal transduction and epigenetic modifications

The Wnt/β-catenin signaling pathway, an evolutionarily conserved pathway that plays a major role in multiple processes, including cell proliferation during development, has been implicated in the toxicity of AgNPs. AgNPs can activate the Wnt/β-catenin signaling pathway, eventually resulting in embryotoxicity in zebrafish [150].

Additionally, AgNPs were shown to disturb female mESCs differentiation by causing premature X chromosome inactivation (XCI) [99], which is responsible for maintaining gene balance between females (XX) and males (XY) during embryogenesis [160]. XCI refers to the inactivation of one of two X chromosomes in the female genome, which plays an important role in governing ESC pluripotency and differentiation by fine-tuning X chromosome-linked gene expression [161,162]. X inactivation center (XIC) in the X chromosome functions as a regulatory part in XCI, and X inactive specific transcript (*Xist*) is crucially responsible for XCI, characterized by *Xist* coating of the inactive X chromosome (Xi) and ensuing transcriptional silencing of Xi, while its antisense *Tsix* takes a chief part in antagonizing *Xist* to maintain the active X chromosome (Xa) [162]. Low concentrations of AgNPs interrupt XCI via the dysregulation of *Xist* and *Tsix* in female mESCs during differentiation, leading to an imbalance in the ratio of *Xist*/*Tsix*, combined with elevated histone modifications, such as histone 3 lysine 27 trimethylation (H3K27me3), which orchestrates X-linked genes closely involved in ESC differentiation [99]. Albeit no observable impairment of AgNPs was found in mESCs, such as self-renewal, propagation, or colony formation, AgNPs can compromise the differentiation of female mESCs via XCI disturbance.

Environmentally-relevant concentrations of AgNPs affected differentiation from ESCs to cranial placode, as evidenced by significant changes in morphology and specific markers [101]. AgNPs were found to inhibit embryonic development partly via the leakage of Ag ions and suppression of the FGF signaling cascade [101]. Although growing mechanisms of the developmental toxicity of AgNPs have been investigated to a certain extent, further research is required on the physical behavior, cellular response, and molecular mechanisms of AgNPs.

6. Perspectives

Nanomaterials are widely used in various fields due to their special physicochemical properties [163,164]. However, the unique antimicrobial properties of AgNPs pose a threat to public health while combating bacteria. The Developmental Origin of Health and Disease (DOHaD) hypothesis suggests that the etiology of adult diseases can be traced back to early life, including the intrauterine period and even previous generations [165]. Studies have demonstrated that AgNPs exposure during pregnancy in rodents can cause fetal developmental disorders and even diseases in offspring [43,46,124]. Embryonic developmental difficulties, such as delayed hatching and larval deformation, have also been observed in experiments with zebrafish embryos [65,70,90]. Neurotoxicity has been a major concern regarding adverse outcomes in rodent offspring [40]. AgNPs have been found in fetal lungs, liver, and kidneys [46,109], yet limited information on their toxicity has been provided. Adverse effects in different tissues in offspring require further investigation. Although many efforts have been made to understand the adverse effects of AgNPs exposure during pregnancy, many clues obtained thus far remain unclear. Research on paternal/patrilineal streamlined lines is scarce to elucidate the developmental risks of AgNPs. Furthermore, while several molecular mechanisms of these effects have been proposed, the information represents only the tip of the iceberg of complex biological processes.

Maternal exposure to AgNPs through various routes can lead to adverse effects during pregnancy, fetal growth, and postnatal development. Only a small fraction of the mechanisms pertaining to the developmental toxicity of AgNPs have been identified, including redox disequilibrium, damage to genetic materials, subcellular dysfunction, and immunoregulatory failure. However, the exact hallmarks or underlying mechanisms are still immature, making it difficult to draw definitive conclusions for prevention and protection. Establishing an integrative framework for the risk assessment of AgNPs to maternal health and filial development is necessary. This is a crucial step before the safe usage of AgNPs-containing medication in the obstetrical field and similar products for babies can be ensured. However, achieving conclusive agreements regarding the window period, dosage threshold, and recognition of hazard mechanisms remains challenging. Therefore, testing strategies must be developed and enriched to regulate nano-developmental hazards, considering physiochemical properties, exposure conditions, maternal health status, and other essential parameters in an integrative framework. The available database is currently insufficient for evidence accumulation and judgment of nano-developmental toxicity. It inadequately serves as a foundation for maternal-infant risk control of diverse types of NPs. Thus, evaluating developmental hazards in *vivo*, *ex vivo*, and *in vitro* representative models can better reveal the health threats of AgNPs to humans and future generations to ensure their use within a safe range.

This study primarily focuses on the perilous effects of AgNPs during pregnancy on offspring; however, numerous other uncertainties and pressing matters demand a more complete comprehension. For instance, (1) certain sensitive exposure windows remain unclear for developmental damage caused by AgNPs during maternal exposure. More supportive data and evidence are needed to determine whether paternal exposure can cause APOs or offspring injury by affecting gamete quality. (2) The mechanisms and influencing factors of AgNPs' translocation into reproductive targets and the attribution of either direct or indirect modes of action remain unexplored. (3) AgNPs can cause multi-systemic adverse effects in offspring, and it is essential to investigate the persistence of such effects across generations. This involves delving deeper into AgNPs-induced intergenerational or even transgenerational damage and the roles played by epigenetic clocks and reprogramming. (4) We have limited knowledge about the complex biological processes involved in the interaction between AgNPs and developmental matrix, and more innovative ideas and crosstalk need to be presented. (5) Although many studies have investigated the transformation and ecotoxicity of AgNPs in the environment, various knowledge gaps and challenges remain in assessing the real-world environmental exposome and health risks of AgNPs. While environmental health risk assessment focuses on understanding the nature of environmental exposure, including exposure concentration and duration, realistic environmental concentrations remain ambiguous and inconclusive due to technical constraints. Therefore, there is a crucial need to develop new instruments capable of monitoring and analyzing actual concentrations of AgNPs in natural environments, including real-time integrated assessment of multiple exposures and dynamic assessment with high temporal and quantitative resolution. In summary, comprehensive insights into the destiny and developmental dangers posed by AgNPs are still significantly limited, demanding substantial

additional evidence.

CRediT authorship contribution statement

Yán Wāng: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Funding Acquisition. **Yapeng Han:** Methodology, Visualization, Validation. **De-Xiang Xu:** Resources, Project Administration.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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