Chapter 6

Genotoxic Effects of Nanoparticles on Gamete Cells and Their Potential Risks for Next Generations

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Summary

Nanoparticles occur in our natural habitats due to biological, physical and chemical processes. Nanoparticles and nanomaterials are increasingly used in food packaging, textiles, electronics, biomedicine, cosmetics (lipstick, sunscreen, etc.), and many aspects of daily life. Therefore, the potential risk of exposure of humans and surrounding organisms to nanoparticles should not be ignored. Nanomaterials are materials with small dimensions and large surface area, as well as other physical and chemical properties, such as polluting metals and charged surfaces, and genotoxic properties. Because of these properties, they can cause mutations and damage to chromosomes. It is required to consider the influence of nanoparticles not only on humans but also on the genetic components of other species in the environment. Recently, adverse effects from exposure of the reproductive system to nanoparticles have emerged, creating the risk of reproductive toxicity. Reproductive toxicity refers to effects that affect the development of healthy embryos, the reproductive cycle, and any stage of pregnancy. The studies about reproductive toxicity of NP is increasing, but research is ongoing. This section focuses on the potential genotoxic efficacy of nanoparticles on germ cells and reproductive systems, and potential risks these effects may cause in the next generations.

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1. Introduction

Nanomaterials are descriptive of materials that have a physicochemical construction of more small than 100 nm (nanoconstruction) and possess biological, chemical or physical properties connected with a nanostructure (Oberdörster et al., 2005).

According to the International Standards Organization (ISO), nanomaterials are divided into two categories: Nanoobjects and nanostructured materials. Nanoparticles (NPs) in nanoobjects are generally classified into 3 groups based on their chemical structures. These 3 groups include carbon based structures like nanotubes and C60-class corridors, nanoparticles like metals or metal oxides, and semiconductor nanocrystals such as CdSe and PbSe known as quantum dots (Krug & Wick, 2011).

Nanoparticles are formed in the nature owing to physical, biological and chemical processes. (Buzea et al., 2007). Nanoparticles and nanomaterials are increasingly used in food packaging, textiles, electronics, biomedicine, cosmetics (lipstick, sunscreen, etc.), and many aspects of daily life (Cotena et al., 2020). The potential risk of mankind and ecological exposure to nanoparticles should not be ignored.

Nanotoxicology is a branch of toxicology that to strive the disadvantageous health effects of nanoparticles. (Donaldson et al., 2004). Factors that may negatively affect human health include NPs' characteristics such as form, inorganic or organic coatings, size, and structure. At the same time, special factors like genetics and diseases also affect the extent of the negative efficacy on human health (Hoet et al., 2004; Nohynek & Dufour, 2012).

Owing to their little particle dimensions and comparatively large surface domain, nanoparticles can join the bloodstream via inhalation, ingestion, dermal uptake, especially outside of applications (Das et al., 2016; Hou & Zhu, 2017). Studies indicated that NPs can enter the cell and cause intracellular oxidative damage by enhance the formation of reactive oxygen radicals (ROS). This can disrupt intracellular biological structures and the normal functions of these structures (Nel et al., 2006). These toxic effects caused by NP lead the cell to apoptosis and can cause conditions like tissue inflammation (Foldbjerg et al., 2009; Li et al., 2010). Moreover, some NPs can cross natural barriers for example the blood-testis barrier, blood-brain barrier (BBB), the placenta and cumulates in various cells (Lan & Yang, 2012; Muoth et al., 2016)

Inhaled NPs may accumulate in the respiratory tract and lungs, because of their high surface reactivity properties, can cause inflammation at the site of

accumulation and cause the produc of reactive oxygen radicals (Hougaard et al., 2010; Møller et al., 2010). Generally, reactive oxygen radicals formation is assumed a major agent in toxic efficacy of nanoparticles (Brohi et al., 2017). ROS molecules are unstable and are characterised by the fact that they do not extend far beyond the region in which they occur (Wells et al., 2005). But, when antioxidant mechanisms fail to keep up with the level of oxidants, oxidative stress rises and triggers or intensifies inflammation which stem from Nps. In this case, a situation occurs in which the area where the mediators or nanoparticles associated with the inflammation occur cannot be limited (Brohi et al., 2017).

In other words, the NPs gain the ability to migrate and inflammatory mediators can also enter the systemic circulation. Through the systemic circulation, NPs can reach organs associated with pregnancy and fetal development and cross barriers such as the placenta, causing oxidative damage and sensitivity in this area. This has indirect negative effects on growing up of fetus (Brohi et al., 2017; Erdely et al., 2011). Particularly in the cells of the placenta, there are receptors called Toll-like receptors (TLR2 or TLR4) are to be included in the inflammatory reagent triggered by respiratory exposure NP (Koga & Mor, 2010; Zhao et al., 2012).

In conclusion, there is evidence that the increase in inflammation and ROS as a result of NP -induced toxicity may have adverse effects on reproduction and development, but these mechanisms cannot be fully explained, and it is reported that further studies are needed to elucidate them (Brohi et al., 2017).

2. Genotoxic Effect of Nanoparticles

Nanomaterials are materials with small dimensions and large surface areas, as well as other physical and chemical properties, such as polluting metals and charged surfaces, and genotoxic properties (Singh et al., 2009). Due to these properties, they can cause mutations and damage to chromosomes (Aloisi et al., 2022).

Genotoxins that cause only genetic changes without cell death can be called classical genotoxins. Carcinogenesis of these genotoxins results in DNA injury. As a consequence of DNA injury, not only the development of cancer is observed, but also significant problems for fertility and health of future generations may occur, as they affect gamete cells (Singh et al., 2009).

DNA injury by NPs can occur directly or indirectly in two ways. Direct interaction of NPs with genetic material results in direct DNA injury. The raise of oxidative damage in cell and the creation of chemical composition

such as ROS leads to indirect DNA injury (de Jesus & Kapila, 2013; Vales et al., 2016).

If the NPs are small enough, they can penetrate the cell membrane and arrive the nucleus, where they bring about damage by interacting with DNA. Even if they accumulate in the cell at a size where they cannot reach the nucleus, they can cause damage by direct contact with DNA if the integrity of the membrane is disrupted during mitosis. In this regard, silica and titanium dioxide nanoparticles have been found to penetrate the nucleus, and have been reported to cause intranuclear protein cluster that can obstruct processes such as cell differentiation, replication, transcription (Singh et al., 2009).

Indirectly, DNA damage can occur when nanoparticles interact with other cellular proteins during cell division. In addition, they cause damage when they trigger cellular responses that cause oxidative damage, intracellular unnatural signalling, inflammation and, causing genotoxicity (Singh et al., 2009).

2.1. Oxidadative Damage and Nanogenotoxicity

Oxidative damage is considered the main reason why nanoparticles cause genotoxic effects. Oxidative damage is the conclusion of an unbalance among the ROS present in the cell and the cell's antioxidant capacity. ROS react negatively with cellular macromolecules like proteins, DNA and lipids compounds in the cell, disrupting cell homeostasis. Examples of adverse reactions of ROS with DNA include strand breaks of DNA, base changes, and DNA cross-links. If these adverse conditions are not corrected, there is a high potential for the onset and progression of carcinogenesis (Singh et al., 2009; Toyokuni, 1998).

Reactive oxygen species are also divided into two type of ROS. One of them primary ROS, could be produced during metabolic duration or by oxygen activation leading to the formation of superoxide anions. Primary ROS do not react directly with polypeptides or DNA. Secondary ROS involves the formation of hydroxyl radicals in the cell as a result of catalysis of hydrogen peroxide with iron or other active transition metals, usually after the Fenton reaction. These hydroxyl radicals are considered to be the primary mediators of DNA damage (Valko et al., 2006).

The formation of hydroxyl radicals may lead to cross-links in chromatin and to changes in free iron ions and purine and pyrimidine bases (Valko et al., 2006; Zastawny et al., 1995). Accordingly, iron-containing nanoparticles be able to cause raised formation of highly reactive hydroxyl radicals by acting

as an additional source of iron in the cell by means of the Fenton reaction (Singh et al., 2009).

In addition to metal catalysts, the surface of nanoparticles brings with it the ability to boost the creation of ROS. Smaller nanoparticles are, have ability to cause higher oxidative stress (Brown et al., 2001; Knaapen et al., 2004). In large quantities studies have indicate that exposure to nanoparticles induces the production of ROS and has genotoxic effects by causing oxidative DNA injury (Gurr et al., 2005; Karlsson et al., 2008; Papageorgiou et al., 2007).

DNA damage following oxidative stress by nanoparticles can trigger several important cellular reply such as DNA repair, cell cycle stoppage or apoptosis. When cellular mechanisms such as DNA repair mechanisms, which prevent permanent mutations that can be caused by genetic damage, are compromised, mutations can occur if the damaged DNA is not repaired and replication occurs. This negatively affects the genetic integrity and life of the cell (Singh et al., 2009).

NP-induced ROS adversely affects the balance of homeostasis of the NP-affected organism. As a result, interleukins like IL-1,6,8 and tumor necrosis factor-a increase the transcription of pre-inflammatory genes. By triggering the nuclear factor kappa B (NF-kB) signal, it creates oxidative stress, and thus events such as DNA injury and apoptosis occur (Brohi et al., 2017; Khanna et al., 2015).

2.2. Nanogenotoxicity Due to Transcription Repression

The most important factor that comes into play in DNA damage is the molecule p53. P53 is a tumor suppressor gene. It shows its action by stopping the cell cycle, triggering the transcription of genes responsible for DNA reparation, or triggering apoptosis to destroy the cell for the utility of the organism if the DNA damage present is too great. This prevents the damage from turning into a mutation (Lane, 1992; Singh et al., 2009).

Nanoparticles are reported to repress transcription of other DNA repair genes (such as BRCA1, Hus1) involved in maintaining genome integrity. This suggests that nanoparticles can potentially lead to more serious genetic problems (Li et al., 2008).

It is essential to take into account the impact of nanoparticles not only on humans but also on the genetic components of other species in the environment. Pollution of water resources in the vicinity of production facilities increases the possibility of exposure to nanomaterials for other

creatures in the environment. Therefore, monitoring endangered species in native wildlife areas for DNA damage from nanotoxicity is essential to prevent adverse efficacy. DNA damage, in particular, is of concern because it may cause hereditary abnormalities and negative efficacy on harmony within the ecosystem (Baun et al., 2008).

3. Genotoxic Effects of Nanoparticles on Male and Female Gamete Cells

3.1. Nanogenotoxicity in the Male Reproductive System

The antenatal term of germ cell growth symbolizes an important viewpoint for epigenetic programming in males. Germ cells and testis have diverse methylation models that may be suitable for sustaining the matchless chromosome construction in male germ cells. Epigenetic changes could beimpacted by ecological determinants that are inherited thanks to the paternal germline and crossed on to subsequent generations. In addition, recent evidence suggests that the antenatal environment can also affect DNA integrity in offspring (Håkonsen et al., 2012; Poma et al., 2014).

Spermatogenesis is a complicated process of germ cell multiplication and differentiation providing to the generation and deliver of spermatozoa from the testis, and it's depends on hormonal interplays among Sertoli cells and germ cells. (Boekelheide et al., 2000). Thight junctions among contigous Sertoli cells form two distinct sections inside of the seminiferous epithelium, an upper and a basal adluminal section. Sertoli cells excrete hormonal and nutritional elements inside the adluminal section, which forms a private microenvironment for germ cell growth and viability.

Exposure of testicular tubules to nanoparticles affects spermatogenesis and the male reproductive system from where it begins in the testicular tubules. The complex cellular arrangement and cellular coactions in the testis create an environment in which spermatogenesis can be affected by nanoscale toxic substances. Numerous in vitro and in vivo researches indicate that many nanoparticles have counter effects on male germ cells (Braydich-Stolle et al., 2005; Braydich-Stolle et al., 2010), and the effect of NP exposure multifarious from species to species, and reduces sperm production (Boisen et al., 2013; Brohi et al., 2017). The reason for the diminished sperm production is owing to the molecular changes that happen as a consequence of the alteration in the expression grades of the genes included in spermatogenesis. In addition, some researches have represented that application of NP to mice caused residue in varied tissues, bearing the

testis and brain. This proposes that some NPs with ease cross the blood testis and blood brain barriers. (Hong, Wang, et al., 2016; Lan & Yang, 2012).

Proposed causes of cellular damage from exposure to nanoparticles include the formation of reactive oxygen radicals (ROS), as mentioned above, and the potential for DNA damage from engineered nanomaterials. Such injury to somatic cells be able to cause inflammation and even malignant cell proliferation, but in the case of germline cells, both types of damage can occur and lead to loss of fertility or inborn fault in the offspring (Poma et al., 2014; Singh et al., 2009).

It was noticed that 25% of the sperm were non-motile when gold nanoparticles were added directly to the sperm, while normal motility was 95% in the group without nanoparticles. When the researchers examined the sperm, they found that the gold nanoparticles penetrated the heads and tails of the sperm and the sperm were fragmented (Ema et al., 2010; Wiwanitkit et al., 2009).

When the impact of another nanoparticle applied directly to the spermatozoa was examined, it was found that the NPs penetrated the spermatozoa, bound to the tail, mitochondria and the acrosome, but had no significant effect on the acrosome response and motility (Ben-David Makhluf et al., 2006).

In male mice were also found to have decreased fertility in response to exposure to NP, increased apoptosis or necrosis of both spermatogenic cells and Sertoli cells, and increased inflammatory reactions (Ritz et al., 2011).

3.2. Nanogenotoxicity in the Female Reproductive System

Oocyte growth and maturation are increasingly vulnerable to differences in the microenvironment, especially to extracellular chemical compounds (Hou & Zhu, 2017). There are some arguments that various NPs may modify the expression levels of genes codifying proteins included in steroidogenesis and genes included in estrogen or progesterone synthesis. (Brohi et al., 2017).

Besides, it is indicated to cause alters in the expression of genes such as cytochrome P450 17A1 (Cyp17a1) and aldoketoreductase family 1 member C18 (Akr1c18), which are to be included in the synthesis and metabolism of estrogen and progesterone. In addition, changes in apoptosis-related genes, increase in inflammatory and immune responses, cell proliferation, increase in oxidative damage and alteratşon in the expression levels of genes to be included in ion transport can be listed as a consequence of longtime

and high-dose be exposed to nanoparticles (Gao et al., 2012). Considering that all these damages and impairments may be interrelated, it is noted that as a consequence of long-term be exposed to nanoparticles, there may be changes in sex steroid hormone levels, a decrease in fertility, and a decrease in pregnancy rates (Brohi et al., 2017).

In different study investigating the efficacy of exposure of some Nps on oocytes, it is reported that the presence of zona pellucida (ZP) can protect the oocyte from oxidative damage and DNA damage at low concentrations, but exposure of np at high concentrations induces oxidative stress and DNA damage is viewed in oocytes with or without zona pellucida. It is found that genotoxicity and aggregation of NPs depend on physicochemical properties of the cell environment, which determine redox modifications and factors such as surface adsorption (Browning et al., 2009; Courbiere et al., 2013).

Studies about toxicity of NP in the female reproductive system mostly involve examining the effects on fertility, embryonic development and perinatal offspring. In addition, the number of studies on reproductive toxicity in in vitro germ cell lines or in vivo animal models is increasing day by day. (Hou & Zhu, 2017).

Some studies report that NPs can enter the cell by endocytosis of granulosa cells, which can lead to changes in hormone levels that result in oocyte dysplasia or abortion of oocyte development in vivo (Hou & Zhu, 2017). In addition, NPs can spread over theca cells and granulosa cells. Hence, affect their normal function and most important one relation to their crucial role in hormone production process (Stelzer & Hutz, 2009).

In vivo studies in female mice showed that be exposed to long time Nps caused an imbalance in the levels of sex hormones and distribution of mineral elements, resulting in decreased pregnancy rate and expression of ovarian genes, as well as increased oxidative stress. Consequently, NPs of a certain size can directly influence hormone excretion in the ovaries, as they can pile up in secretory cells. (Gao et al., 2012; Hou & Zhu, 2017; Melnik et al., 2013).

It has been indicated that NPs be able to pass the blood brain barrier and pile up in the central nervous system. Another potentially harmful effect of NPs causing hormone imbalance is disruption of hormone regulation as a result of induced of the nervous system by NPs. It is stated that NPs could impress the oogenesis process and ovarian health implicitly by damaging the balance of these hormones in addition to the direct effect mentioned in the previous paragraph (Oberdörster et al., 2004).

The efficacy of NPs on hormone excretion occur in two different pathway: 1. NPs pass the BBB and alter the secretion of reproductive system hormones. This affects normal feedback mechanisms. 2. Pathological phenomena can be observed in oocytes and ovaries by NPs entering the ovaries through the circulation and accumulating in cells that play an important role in steroidogenesis. (Hou & Zhu, 2017).

It is also reported that NPs of certain size can enter and pile up in various female germ cells. As a result of these effects of nanoparticles, undesirable changes in the process of oogenesis may occur. These can be listed as the observation of different cell responses in female germ cells like oxidative stress, dysfunction of cumulus cells, apoptosis, disordering of antral formation in oocytes, DNA damage or inhibition of signal carrying among germ cells and somatic cells (Hou & Zhu, 2017). In addition, another study reported that the genotoxic and cytotoxic effects of NPs may be dose-dependent (Di Virgilio et al., 2010).

In studying the influence of np on mouse oocytes in in vitro fertilization (IVF) studies, it was found that np added to the culture medium decreased the fertilization ratio even at quite low concentrations. It was suggested that the reason for this could be genotoxicity or oxidative damage in germ cells because of nps. At high concentrations of NP exposure, it was observed that NPs diffused the cumulus cell layers through out the oocytes' zona pellucida and accumulated in it (Preaubert et al., 2016). Some CeO2 engineered NPs (ENPs) with biomedical properties that are effective in treating endometriosis and protecting the adverse effects of endometriosis on oocytes should be used for limited medical applications because of toxicity, given the results of the above-mentioned in vitro studies (Chaudhury et al., 2013; Hou & Zhu, 2017).

It is also claimed that the accumulation of nanoparticles on the ovaries causes the early onset of oogenesis. Such abnormal processes may lead to the formation of potentially malformed oocytes and dysfunction of the reproductive system. In other words, the accumulation of NP may trigger apoptosis because of the prompt of modifying BCL2 factor (BMF) and mitochondria-related apoptotic pathway (Gao et al., 2012). As mentioned above, most follicles in the ovary undergo a hormonally controlled process of apoptosis during their development, which is regulated by several factors (Hou & Zhu, 2017). As a result of long-term exposure to NPs, it was observed that the expression grades of 288 genes participate in cytokine and hormone pathways were changed in mouse ovaries (Zhao et al., 2013).

4. Developmental Toxicity of Nanoparticles

Adverse effects from exposure of the reproductive system to nanoparticles have recently emerged, posing a risk of reproductive toxicity. Reproductive toxicity refers to effects that interfere with the development of healthy embryos, the reproductive cycle, and any stage of pregnancy. Effects on offspring at any phase of life due to parental exposure are considered developmental toxicity (Brohi et al., 2017).

The quality of gamete cells influences the developmental process. Therefore, a negative effect of nanoparticles on gamete cells or gametogenesis can lead to significant developmental differences (Das et al., 2016). Gametogenesis is a complicated biological process that is sensible to environmental factors. Problems in gamete cells and during gamete cell maturation may affect fertility, induce cancer, and impair embryo development. For example, mutagens resulting from cell impairment can cause inherited gene mutations in germ cells by causing structural and numerical chromosomal damage. Germ cell mutations can result in genetic phenotypic changes, reduced fertility, embryonic death, or congenital malformations and genetic diseases of varying severity, even if the disease does not manifest in subsequent generations (Poma et al., 2014).

In addition, epigenetic changes that happen during gamete cell growth and early embryo growth play a very crucial role in embryo development and successful pregnancy (Khoureiry et al., 2008; Market-Velker et al., 2010). Numerous in vitro studies in animals and humans have demonstrated that diseases of the reproductive system are particularly associated with epigenetic alterations. For this reason, the mechanism of epigenetic reprogramming is important for germ cell development and early embryogenesis. Any problem that may arise from situations such as exposure to nanoparticles in epigenetic mechanisms in the embryonic period may lead to alteration in the expression of related genes, resulting either in the death of the embryo or in permanent diseases that may be transmitted to the next generations.

The placenta is a structure that regulates exchanges between mother and offspring, ensures the continuation of gravidity and embryonic development, and protects the fetus from detrimental situations. While the placental barrier allows the passage of nutrients, hormones, and antibodies, it cannot entirely prevent the passage of all toxic substances. Therefore, developmental toxicity may occur due to transplacental transfer from mother to offspring. Owing to the small size of nanoparticles, they can easily penetrate into the reproductive organs and thus cross the placental barrier easily. Some studies

also show that NP like Au, TiO2, SiO2, carbon (C) may easily cross the placenta (Brohi et al., 2017).

The placenta differentiates after implantation in the uterus wall during pregnancy. Accordingly, as noted in the studies, the effect of NPs may alter be attached on the exposure time of the placenta and fetus, which may alter the embryo's ability to defend against exogenous toxic substances. There are also studies showing that mice in the early stages of pregnancy have higher fetal susceptibility. Nanoparticles were observed in the brain structure of the mouse pups that had received subcutaneous injection of nanoparticles on days 3, 7, 10, and 14 of their pregnancy. Constriction of blood vessels was observed in the hippocampus and cerebral cortex of mouse offspring. These studies suggest that prior to the creation of a functional blood brain barrier, the fetal brain may have little defense against the toxicity of diverse types of NPs (Brohi et al., 2017). Besides, it has been indicated to cause changes in the expression of genes connected with cell death, oxidative damage response, mitochondria, and neurotransmitters, and to affect brain development in the prenatal period (Ema et al., 2010; Fedulov et al., 2008).

It has been reported that the release of metal ions belonging to nanoparticles exposed by inhalation caused to a decline in 17b estradiol levels and an augmentation in mRNA expression level of uterine estrogen receptors, disruption of endocrine mechanism. However, the mechanism of action is not certainly explained. In summary, the possible toxic influence of NP affect both the reproductive function of the offspring and the mothers, and pose a risk to the next generations of offspring exposed directly in utero (Blum et al., 2012; Brohi et al., 2017).

Nanoparticle administration has toxic effects on offspring development, bearing the fetal reproductive system, and results in loss of fertility. In addition to female offspring, NPs were detected by electron microscopy in spermatids, Leydig cells, and Sertoli cells in the testes of 4-day-to 42-day-old male offspring of mothers exposed to subcutaneous nanoparticles at 3 weeks of age. As a result, a reduce in the amount of Sertoli cells, loss of disorganization and integrity in testicular tubules, changes in testicular morphology, and a decrease in daily sperm production were observed. In addition, epididymal sperm motility was found to significantly lower in 42-day-old male offspring (Takeda et al., 2009). It has also been explained that diesel-derived exhaust particles (Diesel Exhaust (DE)) and nanoparticles such as TiO2 transiently suppress Leydig cell proliferation (Hong, Zhao, et

al., 2016). It has also been found to augmentation mutations in the male germline whilst offspring grow up (Boisen et al., 2013).

5. Conclusion

In summary, nanoparticles thanks to their unique properties allow them to provide significant therapeutic benefits in commercial products for example clinical applications, drug delivery systems, cosmetics such as sunscreen lotions or lipstick and textiles they are effectively used in. However, because NPs are non-degradable, in vivo and in vitro researches have indicated the possible for numerous disadventageous health effects from their use or contact (Hou & Zhu, 2017).

The number of studies on reproductive toxicity of NP is increasing, but research is ongoing. While there is evidence that some NPs enter reproductive tissues and organs directly in adult animals and their uteri, it is difficult to make comparisons and definitive conclusions as studies have used various doses and routes of administration.

There is a need to determine minimum doses and exposure pathways for environmental, occupational, therapeutic, and cosmetic uses through human and animal studies of various nanoparticles. Determination of "safe" concentrations of nanoparticles for human and animal health (Brohi et al., 2017).

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