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A Review of *In Vivo* Hepatotoxicity Induced by Quantum Dots

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Abstract: ***Quantum dots (QDs) are being considered to be of high potential value in research, technology and biomedicine. Their unique physico-chemical properties, small particle size and excellent fluorescent properties make them useful in biomedical applications. A great number of studies have shown that QDs are distributed to many secondary organs, liver being the main reservoir. In vivo hepatotoxicity studies show significant discrepancies in results and this review highlights more need of research to elucidate on toxicity mechanisms and need for unifying reliable and realistic reports.***

Keywords: Quantum dots, hepatotoxicity, in vivo toxicity, toxicity mechanisms, oxidative stress

1.Introduction

Semiconductor nanoparticles of different sizes of 1 to 10 nm, belonging to groups IIB-VIA or IIIA – VA elements are called Quantum Dots or QDs. These QDs comprise of two or more kinds of semiconductor materials (Lovric et al, 2005; Wu, Tian, Zhao & Wu, 2013). QDs have broad excitation but narrow emission spectra, making them excellent fluorescent markers. Their sizes can be varied to control their emission spectra; like in CdTe QDs emission wavelength is shifted from 510 nm to 660 nm by increasing particle size 2.5nm to 4 nm (Esteve-Turrillas & Abad-Fuentes, 2013).

Volkov (2015) found QDs have long fluorescent lives than traditional organic dyes. Surface modifications of QDs with various chemicals render them more bio-compatible and less cytotoxic (Resch-Genger, Grabolle et al, 2008). Various applications in medical fields like drug targeting transports, virus detection, fluorescent cell targeting, in vivo tumour imaging are being done with these QDs, (Barroso, 2011; Esteve-Turrillas & Abad-Fuentes, 2013).

Bio-medical applications of QDs make toxicity studies all the more important, especially for liver which is the major metabolic organ of animals. Liver functions include production and secretion of bile and proteins, storage of trace elements and vitamins, synthesis and decomposition of glycogen, phagocytosis of blood pathogens and immune factors production (Fischer, Liu et al, 2006; Hoekstra et al, 2013). Liver also clears exogenous matters of the body (Davies, Jenkins et al, 2013; Fischer, Hauck et al, 2010; W. Zhang et al, 2016) with help of Kupffer cells. Studies showed that QDs enter inevitably into organisms by different pathways and accumulated in liver, probably affecting liver function and histopathology (Cho et al, 2007; Fischer et al, 2006; Zhang et al 2016; Zhu et al, 2017). So, further studies are required for safety evaluation of the QDs for production of safer QDs. The existing studies on in vivo hepatic toxic effects were reviewed to help in further studies.

2.In vivo hepatotoxicity of quantum dots:

Animals like rodents, zebra fish and *Caenorhabditis elegans* have been studied for QDS in vivo toxicities. Very few researchers have used primates like rhesus monkeys. The toxicity tests were primarily used to study distribution process, metabolism and excretion and possible damages occurring in organ tissues.

2.1. Accumulation of quantum dots in liver:

Regardless of exposure routes, QDs have a tendency to accumulate in reticular endothelial systems like liver, kidneys, spleen and lungs (Haque et al, 2013; Su et al, 2011; Yang, Lan et al, 2014). Intravenous and intraperitoneal exposure of CdSe/CdS QDs in rhesus monkeys and mice have shown liver to be the main target organ for QDs accumulation. Hepatotoxicity can not be ignored because liver is the main organ concerned with accumulation and metabolism of organisms.

2.2. Quantum dots seems to have no harmful effects on hepatic function:

Intravenous injection of 5 nmol of CdTe QDs and CdTe/SiO_2 QDs on the BALB/C mice resulted in their death after 30 days after exposure but both QDs would not cause any histopathological changes or damage in the liver (Sadaf et al, 2012). Studies on distribution, metabolism and elimination of AgSe QDs modified with three different types of surface modifiers yielded similar results. Three QDs (QD-PEG, QD-MEA, QD-MPA) accumulated in liver and spleen after 7 days of exposure by intravenous injection in mice and were significantly converted to Ag and Se. Only QD-MEA was responsible for oedema and necrosis in liver on 28^{th} day (Tang et al, Fan et al, 2016). Mu et al, 2017 found that black phosphorous QDs caused apoptosis of liver cells but apoptotic cells were absent after 7 and 30 days. The complexities of internal environment of organisms yield different results from in vitro experiments. During transportation by blood, blood proteins form protein corona on QD surfaces. This affects metabolism and redistribution of QDs due to cell phagocytosis (Feliu et al, 2016). The immune system also works to reduce the potential toxic effects of QDs (Fischer et al, 2010). Though QDs were found to accumulate in Kupffer cells and endothelial sinusoidal cells in hepatic sinusoids by Liang et al, yet, in another study by Liang et al, 2015, it was found that CdTe/CdS-MSA QDs did not

assimilate in hepatocytes after intravenous administration into Wistar rats.

2.3. Inflammatory response by QDs:

Studies had shown that CdTe/ZnS (40 and 160 pmol per mouse) QDs induced an elevated expression of proinflammatory factors like IL-6 and TNF-α (Lin et al, 2011). Other studies have also shown that QDs have no significant histo-pathological damage in liver but mild inflammatory responses have been found to occur (Haque et al, 2013; Lin et al, 2011; Liu et al, 2013; Lu et al, 2016; Stanca et al, 2013). QDs lead to NLRP3 inflammasomes activation and increased secretion of IL-1β in the liver (Lu et al, 2016). These studies have related Kupffer cells with inflammatory functions in hepatocytes as QDs were mainly ingested by Kupffer cells and blood sinus endothelial cells after entering the liver (Lin et al, 2011). Very small number liver parenchymal cells phagocytize QDs (Liu et al, 2013; Manshian et al, 2015). QDs can be used for diagnostic purposes, so, further studies are essential in appropriate animal models to estimate damages caused in lesions of organs by QDs.

2.4. Oxidative stress:

Oxidative stresses caused by QDs in vivo have been found in many studies (Lin et al, 2011; Zhang et al, 2015). QDs lead to significant increase in the levels of ROS or-OH and caused changes in glutathione peroxidase, CAT, SOD concentrations and activities (Serba at al, 2015; Wang et al, 2016; Y Yang et al 2014; Yang et al, 2015; Zhang et al, 2015).

2.5. Other toxicities:

Some studies have shown QDs can cause significant liver damage, tissue disorders and liver fibrosis (Fan et al, 2016; Stanca et al, 2013; M. Wang et al, 2016). Degeneration of hepatic cells and a significant increase of functional indicators of aspartate aminotransferase and alanine aminotransferase were observed after 30 days of exposure of MPA-CdTe/CdS QDs (0.1-0.3 nmol per mouse) by intravenous injection (Fan et al, 2016). In another study on Gibel carp with Si/SiO_2 QDs (2 mg/kg body weight), Stanca et al (2013), observed pathological changes in liver like hepatic macrophage hyperplasia, fibrosis, alkaline granulocyte aggregation and decreased levels of GSH and thiol containing proteins. More studies are required to explore the wide gap in in vivo studies results. This might help in illuminating the details of QDs interaction with liver cells and disruption of liver by their mechanism of action.

3.Parameters influencing hepatotoxicity of Quantum Dots:

Discrepancies in results of QDs in vivo studies may be due to various parameters like different sizes, types, dose, exposure routes, exposure time and animal models. Presently, prevalent research interests converged on factors like types, sizes and surface modifications of QDs. Other factors have been rarely studied and to be explored more.

3.1. Size and toxicity:

Most researches have shown smaller QDs have greater toxicities (Y. Tang et al, 2013; Peng et al, 2013). The size of QDs affects in vivo distribution (Chang et al, 2012; Su & Sun, 2013; W. Zhang et al, 2016). When QDs entered nucleus of cells, DNA was more vulnerable to damage. However, effect of QD size on hepatotoxicity is still under discussion. As QDs have smaller sizes than nanomaterials, their results may not apply to QDs.

3.2. Surface chemistry and toxicity:

Cd containing QDs release Cd^{2+} ions. This aspect makes them toxic and limits their biomedical applications. So, surfaces of synthesized QDs were coated with molecules of functional groups to inhibit Cd^{2+} ions release and reduce toxicity. Their sizes increase after surface coating and reduction of toxicity was observed (Liang et al, 2015; Sadaf et al, 2012; Yang et al, 2014). A study by Yang, et al, showed ZnO QDs could increase antioxidant activities like CAT/GSH-PX, SOD and MDA), whereas ZnO-PEG QDs had little antioxidant activity. Also, ZnO-PEG QDs were lodged in lysosomes but ZnO QDs were evenly distributed in lysosomes. Intracellular distribution differences alter toxicities. Distribution of positively charged negatively charged and neutral QDs in vivo were inconsistent. The positively charged QDs were mainly in the kidneys and the other two were mainly in spleen and liver (Q. Liu et al, 2015; Y. Tang et al, 2013). Positively charged QDs had the highest hepatotoxicity and the toxicity was minimum for neutral QDs.

3.3. Quantum Dots types and composition:

Synthesis of Cd free QDs like III AV A and IV group elements like InP/ZnS QDs, Silicon QDs, Carbon QDs have shown more bio-compatibility and less toxicity (Volkov, 2015; Wang et al, 2016; Wu et al 2013). Surface modifications have also reduced toxicities (S. Tang et al, 2013). For the more biocompatible QDs, sub-toxic dosage effects need to be studied more, exposure time should also be addressed. Pro-inflammatory cytokines except TNF-β were significantly increased in human hepatocytes which was an indicator of inflammatory response caused due to QDs (Smith et al, 2012).

3.4. Other factors:

For in vivo studies complexities of organisms must be considered along with physico-chemical properties of QDs. Presently, in vivo exposure pathway was mainly intravenous injection, a few studies involved abdominal exposure by intraperitoneal injection. The QDs enter the liver through venous pathway, come in contact with macrophages and sinusoidal endothelial cells (Liang et al, 2015). Kupffer cells and liver sinusoidal endothelial cells take up QDs selectively, for example, CdTe/CdS-MSA QDs, after accumulation in liver sinusoids. This probably reduced toxic effects on other hepatocytes (Liang et al,

2015; Chen, Xue & Sun, 2013; Fischer et al, 2013; Zhu et al, 2017). This study may explain the absence of observations of toxicities in liver like damaged histo-pathological functions but inflammatory responses were observed up to a certain extent.

4.Conclusion

In vitro studies have demonstrated certain QDs are toxic to certain cells and generate ROS and free Cd^{2+} ions release in Cd containing QDs seem to be more toxic (S. Tang, V. Allagadda et al, 2013). The in vitro studies revealed hepatotoxicity but many controversial results exist for in vivo studies on liver toxicity, closely related to animal models, exposure dose and time and types of QDs. Also, biological environment influences distribution, metabolism and exclusion of QDs in animal models. Some QDs caused mild inflammatory effects, oxidative stress at gene or protein levels, some hold unclear toxicity and few QDs have caused liver pathological changes or liver dysfunction.

There is an urgent need for more research studies on hepatotoxicity of QDs, though; there has been a rise in experiments and studies of QDs toxicities over the past decades. Based on this review, these are some possible research options for further studies:

- Systematic in vivo studies of QDs on liver toxicity can be achieved.
- There is a need of combined in vitro and in vivo studies to unravel the inter-related relationships between certain parameters like surface chemistry, QD sizes, charge, chemical composition and hepatotoxicity.
- Future in vivo hepatotoxicity studies need to elucidate the QDs distribution, interaction with different liver cells and inductor role of non-parenchymal hepatocytes like Kupffer cells and hepatic sinusoidal endothelial cells in hepatotoxicity.

Understanding deleterious effects of QDs on liver cells can be done by establishing appropriate liver disease animal models to assess the toxic effects of QDs along with practical applications.

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