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Nano-sized iron particles may induce multiple pathways of cell death following generation of mistranscripted RNA in human corneal epithelial cells

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ABSTRACT

Iron is closely associated with an ambient particulate matters-induced inflammatory response, and the cornea that covers the front of the eye, is among tissues exposed directly to ambient particulate matters. Prior to this study, we confirmed that nano-sized iron particles (FeNPs) can penetrate the cornea. Thus, we identified the toxic mechanism of FeNPs using human corneal epithelial cells. At 24 h after exposure, FeNPs located inside autophagosome-like vacuoles or freely within human corneal epithelial cells. Level of inflammatory mediators including nitric oxide, cytokines, and a chemokine was notably elevated accompanied by the increased generation of reactive oxygen species. Additionally, cell proliferation dose-dependently decreased, and level of multiple pathways of cell death-related indicators was clearly altered following exposure to FeNPs. Furthermore, expression of gene encoding DNA binding protein inhibitor (1, 2, and 3), which are correlated to inhibition of the binding of mistranscripted RNA, was significantly down-regulated. More importantly, expression of p-Akt and caspase-3 and conversion to LC3B-II from LC3B-I was enhanced by pretreatment with a caspase-1 inhibitor. Taken together, we suggest that FeNPs may induce multiple pathways of cell death via generation of mistranscripted RNA, and these cell death pathways may influence by cross-talk. Furthermore, we propose the need of further study for the possibility of tumorigenesis following exposure to FeNPs.

1. Introduction

The cornea is the transparent tissue that covers the front aspect of the eye and functions as the predominant refractive surface that helps focusing images on the retina (Loh et al., 2009). The eye can be also directly exposed to foreign bodies, and the cornea protects the inner eye against these foreign bodies. Therefore, when the cornea was injured, foreign bodies may penetrate deeper into the eye resulting in more extensive eye damage. Meanwhile, when foreign bodies enter the body, the host's immune system recognizes and takes it up, to remove it from the body. However, the cornea has no blood vessels and receives nutrients and oxygen through diffusion from the tear fluid on the outside surface. Additionally, the cornea is very sensitive to numerous physical and chemical factors including touch, temperature, and chemicals.

Growing evidence suggest that ambient particles can induce harmful effects in the eye. House dusts induced toxicity via oxidative stress, inflammatory response, and mitochondrial dysfunction in primary human corneal epithelial cells (Xiang et al., 2016). Diesel exhaust particles also clearly decreased viability, proliferation, and secretion of IL-8, but not IL-6, in human epithelial cells of the cornea and conjunctiva, although the detailed mechanism was different for each cell (Tau et al., 2013). Additionally, nanoparticles have recently received tremendous concern as a novel drug delivery system to improve both the bioavailability in the retina and the permeability of therapeutic molecules across the barriers of the eye (Diebold and Calonge, 2010; de Campos et al., 2004; Zarbin et al., 2013; Hu et al., 2012). As an example, cell labeling with superparamagnetic iron oxide nanoparticles assisted transplantation of human corneal endothelial cells, by attaching the posterior corneal stroma without adverse effect on the cell function (Bi et al., 2013).

Iron is one of the most abundant elements on earth by mass. Iron is

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