Antioxidants effects of Platinum Nanoparticles: A Potential Alternative Treatment to Lung Diseases

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INTRODUCTION

Nanotechnology is growing exponentially with the creation of a variety of products from nanoparticles like silver, titanium, gold, lead, zinc, silicon and platinum. Recent statistic in October, 2013 stated that 1628 of nanotechnology consumer products has been created including 788 health and fitness products (Anonynms, 2013). Nanomaterials can be classified into a few aspects but the main classification is based on the composition and shape (Nair, 2009). Nanomedicine lies under nanotechnology that widely explored by researchers to be one of the solutions in lung cancer’s treatment. Metal nanoparticles such as titanium, gold, silver and platinum have been proven to be a potential antioxidant (Table 1). Whilst many extensive researches only focused on the first three metals, platinum nanoparticles (PtNPs) has been given less attention. The presence of antioxidants such as PtNPs is proposed to reduce the effect of reactive oxygen species (ROS). For years, PtNPs have been only used as a catalyst for their high conductivity and reactivity properties in medicine (Cheng et al., 2009). Bimetallic nanoparticles of gold and platinum able to quench superoxide anion and hydrogen peroxide (Kajita et al., 2007). Preliminary results suggested that by giving intranasal administration of PtNPs to a secondhand smokers can inhibit depletion of antioxidant capacity, NFkB activation and neutrophilic inflammation in the mice lung (Onizawa et al., 2009). In addition, the use of PtNPs have been significantly involved in cosmetics and medicine production as an antioxidant (Onizawa et al., 2009). Previous studies report that the PtNPs can act as catalase and superoxide dismutase (SOD) activities which are important antioxidant enzymes against free radical damages. A mixture of palladium and platinum nanoparticles (PAPLAL) accelerated wound healing in aged mice and attenuate skin atrophy in Sod1−/− mice (Shibuya et al., 2014). PtNPs has significantly reduced the superoxide anion production in an ischemic stroke mice model (Takamiya et al., 2011). This proves that PtNPs produce protective effects against ROS and may play a role in oxidative stress associated with lung diseases. Recently, millions of people have suffered from respiratory related diseases and cancers which contribute to the main lethality worldwide. Cancers which are the abnormal growth of cells can invade other organs in the body at upper stages. Therefore, cancer biomarkers are needed to indicate the progression of the cancers.

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PtNPs may act as electrochemical biosensor to enhance the detection sensitivity and higher accuracy as compared to conventional methods such as ELISA, chromogenic and fluorescence or surface plasmon resonance (Liu, Wang, et al., 2014).

Table 1: The use of metal nanoparticles in nanomedicine.

<table>
<thead>
<tr>
<th>No.</th>
<th>Metal Nanoparticles</th>
<th>Roles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Titanium dioxide nanoparticles</td>
<td>Induce transient pulmonary inflammation but not lead to chronic lung disorder</td>
<td>(Yoshiura et al., 2015)</td>
</tr>
<tr>
<td>2</td>
<td>Titanium dioxide nanoparticles</td>
<td>Induce apoptosis and DNA damage in A549 cells</td>
<td>(Wang et al., 2014)</td>
</tr>
<tr>
<td>3</td>
<td>Gold nanoparticles</td>
<td>Mainly used in gold nanoprobe-based technique which is better than PCR based techniques for detecting lung cancer biomarker</td>
<td>(Daraee et al., 2015)</td>
</tr>
<tr>
<td>4</td>
<td>Glucose-coated gold nanoparticles</td>
<td>Enhance better cancer killing compare to X-ray or AuNPs alone</td>
<td>(Hu et al., 2015)</td>
</tr>
<tr>
<td>5</td>
<td>Gold nanoparticles</td>
<td>Reduce cell viability and induce oxidative stress in 2C32 myoblast cells</td>
<td>(Wahab et al., 2014)</td>
</tr>
<tr>
<td>6</td>
<td>Silver and gold nanoparticles</td>
<td>Increase ROS and deplete antioxidant enzymes status in erythrocytes and tissues</td>
<td>(Shrivastava et al., 2014)</td>
</tr>
<tr>
<td>7</td>
<td>Silver nanoparticles</td>
<td>Antimicrobial agents</td>
<td>(Franci et al., 2015)</td>
</tr>
<tr>
<td>8</td>
<td>Silver nanoparticles</td>
<td>Induce oxidative stress in bone marrow cell of rats</td>
<td>(Patilova et al., 2015)</td>
</tr>
<tr>
<td>9</td>
<td>Silver nanoparticles</td>
<td>Induce rat motor dysfunction</td>
<td>(Yin et al., 2015)</td>
</tr>
<tr>
<td>10</td>
<td>Silver nanoparticles</td>
<td>Small size AuNP are cytotoxic to BEAS-2B human lung cells</td>
<td>(Gliga et al., 2014)</td>
</tr>
<tr>
<td>11</td>
<td>Silver nanoparticles</td>
<td>Induce strong toxicity, reduce cell viability and increase LDH release in A549 human lung cells</td>
<td>(Lee et al., 2011)</td>
</tr>
</tbody>
</table>

Surgery, chemotherapy and radiotherapy has been the most common practices to treat cancers. Chemotherapy is considered the most successful when a sufficient concentration of effective drug concoctions are delivered to the tumor cells without causing intolerable toxicity effects to the patients. (Mohammadi et al., 2013). In radiotherapy treatment, radiosensitizers are used in order to make tumor cells more sensitive to the therapy thus killing the cancer cells. AuNPs have been used as a radiosensitizer together with x-ray radiation. However, PtNPs can be used with combination of hadron therapy that can enhance double strands breaking DNA better than AuNPs with x-ray (Porcel, et al., 2010). This can be complementary to DNA glycosylase mechanism to accelerate the reconstruction of new DNA, as its activity in lung cancer tissues are relatively low in comparison to the normal lung tissues (Sarker et al., 2014). A small size of 20nm has shown an antioxidant effect of PtNPs, which exhibit better catalytic activity than larger particles because of their larger surface area and the presence of atoms on the surface (Konieczny et al., 2013; Magdolenova et al., 2013). Nevertheless, the use of appropriate size needs to be addressed to avoid a toxicity effect to certain organs. The size that toxic to the cell is different among various metal nanoparticles. PtNPs exposure of less than 1 nm in mice can induce renal injury, but the effects of this injury can be reduced by increasing the size nanoparticles (Yamagishi et al., 2013).

Meanwhile, 1 nm PtNPs has been proven to scavenge superoxide anion radical as compared to 5 nm (Hamasaki et al., 2008). However, smaller size of PtNPs did not influence in the gene expression in various organs of rats (Katao et al., 2011).

Table 2: Roles of platinum nanoparticles in nanomedicine.

<table>
<thead>
<tr>
<th>No</th>
<th>Platinum related research</th>
<th>Roles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palladium and platinum nanoparticles</td>
<td>Treat aging-related skin diseases</td>
<td>(Shibuya et al., 2014)</td>
</tr>
<tr>
<td>2</td>
<td>Platinum nanoparticles</td>
<td>Scavenge ROS on blood vessel mimicking microfluidic chip</td>
<td>(Zheng et al., 2014)</td>
</tr>
<tr>
<td>3</td>
<td>Platinum nanoparticles</td>
<td>Inhibit DNA double-strand scission by degradation of ROS</td>
<td>(Panikkanvala pill et al., 2013)</td>
</tr>
<tr>
<td>4</td>
<td>Platinum nanoparticles</td>
<td>Anti-inflammatory effects on lipopolysaccharide in RAW 264.7 macrophages</td>
<td>(Rehman et al., 2012)</td>
</tr>
<tr>
<td>5</td>
<td>Platinum nanoparticles</td>
<td>Neurobehavioral and neuroprotective effects on ischemic stroke</td>
<td>(Takamiyai et al., 2011)</td>
</tr>
<tr>
<td>6</td>
<td>Platinum nanoparticles</td>
<td>Decrease ROS production from  UV-light-induced epidermal inflammation</td>
<td>(Yoshhiisa et al., 2010)</td>
</tr>
<tr>
<td>7</td>
<td>Platinum nanoparticles</td>
<td>Inhibit pulmonary inflammation</td>
<td>(Onizawa et al., 2009)</td>
</tr>
<tr>
<td>8</td>
<td>Platinum nanoparticles</td>
<td>Decrease oxygen species in cells and increase cells viability during stress</td>
<td>(Zhang et al., 2009)</td>
</tr>
<tr>
<td>9</td>
<td>Platinum nanoparticles</td>
<td>Scavenge superoxide anion and hydroxyl radical</td>
<td>(Hamasaki et al., 2008)</td>
</tr>
<tr>
<td>10</td>
<td>Platinum nanoparticles</td>
<td>Extend the lifespan of C. elegans</td>
<td>(Kim et al., 2008)</td>
</tr>
<tr>
<td>11</td>
<td>Gold and platinum nanoparticles</td>
<td>Scavenge superoxide anion and hydrogen peroxide</td>
<td>(Kajita et al., 2007)</td>
</tr>
</tbody>
</table>

Where studies on the identification of PtNPs potential in nanomedicine are still ongoing, we cannot miss any possible side effects that may be caused by PtNPs. To date, findings have shown that no hydroxyl radicals was formed when PtNPs are mixed with hydrogen peroxide (Okamoto et al., 2012). PtNPs also produce a better result in reversing oxidative stress in bronchiolar cell lines as compared to another metal nanoparticles (Schmidt et al., 2007). PtNPs treatment to the adherent cells human have shown no cytotoxicity effects to various cell lines including diploid embryonic lung fibroblasts (TIG-1), human diploid fibroblasts (WI-38), human diploid embryonic lung cell lines (MRC-5), cervical carcinoma cells (HeLa) and human hepatocellular carcinoma cell lines (HepG2) (Hamasaki et al., 2008). To further demonstrate its safety, PtNPs have been used as a commercial supplement product after being approved by Ministry of Health, Labour and Welfare of Japan (Onizawa et al., 2009). Whilst the effects of PtNPs in vitro are promising, its activation through a specific mechanism to treat lung diseases needs to be elucidated. Hereby, we are proposing the antioxidant properties of PtNPs in reversing oxidative stress through epithelial sodium channel...
(ENaC) especially in the lung cells. Earlier studies have demonstrated that inflammation of the lungs may cause reduction in ENaC activity that lead to a severe edema prognosis (Suzuki et al., 2004; Dagenais et al., 2005). Therefore, ENaC is suggested as an important indicator to link with the redox status upon treatment of PtNPs.

**EPITHELIAL SODIUM CHANNEL (ENaC)**

ENaC is expressed in the apical plasma membrane of lung epithelial, kidney, tongue and bladder. ENaC plays an important role in mediating Na⁺ absorption in the epithelial cells. In lung cells, increased pulmonary edema has shown to be reduced thus affecting Na⁺ absorption through the alveolar ENaC (Bhalla & Hallows 2008). ENaC is composed of three homologous subunits which are alpha (α), beta (β) and gamma (γ) (Figure 1). Each subunit has an amino (N) and carboxyl (C) intracellular instead of two membrane domains connected by a large extracellular loop (Hughey et al., 2004). Each subunit has homologous structure and the three subunits share 30% similarity in amino acids sequences. All three subunits are required to form a fully functional channel. α-subunit of ENaC is the main pore formation subunit while β-ENaC and γ-ENaC are based on the selection. α-ENaC can be constituted alone however maximum potential can be seen when all subunits were expressed altogether (Bruns et al., 2003, Ismail et al., 2014).

![Fig. 1](image-url)

**PKC PATHWAY**

Protein kinases are enzymes that regulate the function of proteins through the addition and elimination of phosphate groups. This will cause changes in enzyme activity. Some of the protein kinases that involved in ENaC expressions are PKA (Blazer-Yost et al., 2003; Snyder et al., 2004; Liang et al., 2010; Ismail et al., 2014), PKB (Mansley & Wilson 2010; Watt et al., 2012; Ismail et al., 2014) and P-13 kinase (Mansley & Wilson 2010; Watt et al., 2012; Ismail et al., 2014). Another important protein kinase that involves in carcinogen signalling pathways is Protein Kinase C (PKC). PKC regulates the function of other proteins through phosphorylation of hydroxyl groups on the amino acid serine (Ser) and threonine (Thr) (Figure 2). Bao et al., (2014) reported that phosphorylation of Myristoylated alanine-rich C-kinase (MARCKS) by PKCα causes this protein to leave the membrane and does not sequester PIP₂ to ENaC thus causing open probability of ENaC to decrease. PKC signaling through activation of MAPK1/2 in A6 cells has lead to the degradation of γ-ENaC (Booth & Stockand 2003). PKC also involves in the regulation of lung liquid volume and inhibit ENaC activity. When PKC activators, phorbol 12-myristate 13-acetate (PMA) and Ca²⁺ ionophore ionomycin generate simultaneously into the lungs, the movement of transepithelial fluid lungs decreases significantly but the decreases is blocked by PKC inhibitors, chelerythrine chloride and GF109203X (S soukup et al., 2012). Hypoxia-inducible factor (HIF) also regulates heme-oxidized IRP2 ubiquitin ligase IL (HOIL-IL) that function similarly as PKCζ ubiquitin ligase to promote lung tumor growth (Queisser et al., 2014). Thus, research nowadays need to explore more about the inhibitor of the PKC isoforms that can be applied to chemotherapy and radiotherapy without giving adverse effects to the patients (Fan et al., 2013). The upregulation of PKC will reduce the expression of ENaC. M2 transmembrane protein can enhance ROS production and stimulate PKC but the protein can reduce ENaC expression by promoting endocytosis and proteosome degradation (Lazarik et al., 2009). Thus, antioxidant characteristic of PtNPs will help to counteract the oxidative stress formed during the inflammation thus down-regulate the PKC and ENaC.

ENaC protein that consist of N and C terminals together play a role in the surface of the cells. N terminal of α-ENaC is required for maximum activity, while β-ENaC and γ-ENaC are required in determining the half-life channel (Staub et al., 1997). Amino acids in each subunit in the extracellular domain distinguishes ENaC function to ensure the utility domain in which each subunit can interact with the extracellular solution. This involves the process of glycosylation (Rotin et al., 2001) and amiloride binding (Benos 1982) which specifically exists in the α-subunit of ENaC (Berdiev et al., 1998). C-terminal transmembrane domain face extracellular serine-proteases which leads to the activation of ENaC which linked by the linker region located in the catalytic domain to allow ENaC interaction against other proteins on the cell surface (Hooper et al., 2001). This region also contains internalization proline-rich (PY) motif sequences. Deletion of PY-motif will enhance ENaC activity and this will lead to Liddle syndrome symptoms (Abriel et al., 1999; Rotin et al., 2001). ENaC stability can be regulated by lysine acetylation as this will antagonize ENaC ubiquitination (Butler et al., 2015). Duration for the channel to open and the density of functional channels are two important factors that can alter the regulation of ENaC. The open probability of ENaC increases three-fold in PKC-α knockout mice compared to wild type mice (Bao et al., 2014). The current finding has shed some light on the relationship of PKC and ENaC activity.
CONCLUSION

PtNPs may provide as an alternative carrier drug to oxidative stress-related diseases through more effective methods and to produce less effects to the body system. Thus, it is worthy to study the mechanistic pathway related to PtNPs hence to strengthen its contribution to the nanomedicine field. The study on ENaC is important to understand further about the rate of fluid absorption in the lungs and thus reducing respiratory problems caused by oxidative stress. PtNPs need to be demonstrated as an antioxidant agent that can reduce the effects of ROS. PtNPs may reverse the oxidative imbalance and in subsequent will affect ENaC activity by downregulating PKC in the lung cells thus will act as a potentially alternative treatment to treat lung diseases.

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