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The College of Graduate Studies and the College of Medicine and Health Sciences Cordially Invite You to a

PhD Dissertation Defense

Entitled

PULMONARY AND SYSTEMIC PATHOPHYSIOLOGICAL IMPACT OF SILVER NANOPARTICLES: EFFECTS OF COATING, TIME AND DOSE

by

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Date & Venue

1:00 PM

Monday, 20th of January 2020

Time: 13:00 to 14:00 p.m.

Yanah Theater, College of Medicine and Health Sciences, 2nd floor Lecture Theater (Female side)

Abstract: Nanotechnology is rapidly developing, and the engineered materials (ENMs) are utilized in a wide array of end user products owing to their unique physiochemical properties. Of the various forms of ENMs, silver nanoparticles (AgNPs) have gained much attention for potential uses in biomedical, pharmaceutical, and many other industrial applications entailing human exposure. Among the various routes, pulmonary exposure to AgNPs has received increased interest due to their potential to cause pulmonary injury, cross the alveolar-capillary barrier, and distribute to remote organs. However, the mechanism by which pulmonary exposure to AgNPs may induce pathophysiological effects on the cardiovascular system and other major remote organs (including liver, kidney, spleen and brain) is not well understood. Thus, the primary objective of this dissertation was to evaluate, in mice, the coating [(polyvinylpyrrolidone (PVP) and citrate (CT)], time (1 day and 7-days) and dose-dependent (0.05, 0.5 and 5 mg/kg) effects of pulmonary exposure to 10 nm AgNPs, on the cardiovascular system and other major organs including liver, kidney, spleen and brain. Moreover, since AgNPs are able to translocate from the airways into the bloodstream, they can, consequently, interact with circulatory cells such as erythrocytes. However, information regarding the pathophysiological effects and possible mechanism of action of AgNPs on the erythrocytes are still inadequately studied. Hence, to address this, we evaluated the effects of PVP- and CT- AgNPs (10 nm) at three different doses (2.5, 10, and 40 µg/ml) on mouse erythrocytes *in vitro*. For the *in vivo* experiments, AgNPs exposure in mice was achieved by single intra-tracheal instillation and various cardiac and systemic endpoints were assessed including thrombosis, inflammation, oxidative stress, DNA damage and apoptosis following 1 and 7-days of exposure. Pulmonary deposited AgNPs induced dose-dependent cardiovascular effects including thrombosis, oxidative stress, inflammation, coagulation and apoptosis, with some of the effects persisting even after 7-days post-exposure. A biodistribution of AgNPs showed that, besides the presence of AgNPs in the lung, these nanoparticles were also found in the spleen, liver and to a lesser extent in the kidney, heart and brain. In addition, both PVP- and CT- AgNPs induced inflammation and oxidative stress in these latter organs as evidenced by significant elevations of tumor necrosis factor α, interleukin-6, glutathione, total antioxidants, nitric oxide and 8-isoprostane, as well as DNA damage and apoptosis in lung, heart, liver and brain, as shown by 8-hydroxy-2deoxyguanosine and TUNEL assay. Our *in vitro* study revealed that both coating AgNPs induced significant and dosedependent hemolysis, oxidative stress and increase cytosolic Ca^{2+}, annexin V binding and calpain activity. In conclusion, our data showed that AgNPs deposition in the lungs induced pulmonary inflammation and oxidative stress. Secondly, the particles translocated and distributed to the remote organs including heart, liver, kidney, spleen and brain and caused alteration in oxidative stress markers, inflammatory cytokines, DNA damage and apoptosis. Thirdly, AgNPs induced prothrombotic actions, and altered coagulation markers. Fourthly, *in vitro* data indicated that both PVP- and CT-AgNPs induced erythrocyte hemolysis and eryptosis. Overall, these *in vivo* and *in vitro* results, not only reinforced the previously established mechanisms of DNA damage caused by reactive oxygen species, resulting in cellular dysfunction and apoptosis, but also provided a novel mechanistic insight into the pathophysiological effects and tissue distribution of pulmonary exposed AgNPs

Keywords: Silver nanoparticles, oxidative stress, inflammation, eryptosis, apoptosis, DNA damage.