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DNA DAMAGE BY NANOPARTICLES

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BACKGROUND

Nanoparticles (NPs) have provided very significant technological advancements in nanomedicine in the areas of bactericidal agents in food processing, protective skin sunscreens, and the treatment of cancer tumors. However, there is a darkside. Over the past decade, experiments [1-7] have suggested NPs are a health risk by inducing DNA damage that is known to possibly lead to cancer

But what is the mechanism of DNA damage by NPs?

The oxidative stress paradigm correlates DNA damage by the number of reactive oxidative species (ROS), e.g., peroxides and hydroxyl radicals produced with the surface area of < 100 nm NPs. But particulate matter (PM) comes in all sizes that hold the oxidative stress paradigm in question. Electron spin resonance (ESR) comparisons of coarse PM 2.3-10 microns from air pollutions samples have been shown [8] to produce greater numbers of hydroxyl radicals than the fine PM <2.5 microns, but the mechanism was not defined.

Electromagnetic (EM) mechanisms based on the observation [9] that DNA damage by <100 nm NPs mimics [9] the very same pathways of conventional sources of EM radiation. On this basis, the hypothesis was formed [10] that NPs somehow produce their own EM radiation at least at ultraviolet (UV) levels, albeit at low intensity. In fact, low intensity EM radiation from NPs at UV levels is consistent with the theory [11] of QED induced EM radiation. QED stands for quantum electrodynamics. By this theory, fine < 100 nm NPs absorb low frequency thermal kT energy in the far infrared (FIR) upon collisions with solution water molecules. Here, k is Boltzmann's constant and T is absolute temperature. Since quantum mechanics precludes specific heat in NPs, absorbed kT energy cannot be conserved by an increase in temperature, and therefore is induced by QED to be frequency up-converted from the FIR to the EM frequency of the NP, usually beyond the UV. But the quasi-bound EM confinement of the NPs allows the UV to leak and thereby damages nearby DNA.

.. By QED induced radiation, coarse PM does not produce UV, but rather EM radiation in the near infrared (NIR) or an even lower frequency. By itself, NIR and lower radiation does not damage DNA, but compared to the FIR available from the collisions of water molecules enhances the UV from the < 100 nm NPs. What this means is the oxidative stress paradigm based on < 100 nm NPs is still a valid DNA damage mechanism, but requires qualification for enhancement of DNA damage by coarse PM.

In summary, QED induced EM radiation provides NPs with a remarkable natural source of low level continuous EM radiation that produces ROS and thereby enables the NPs to function as an antibacterial agent while at the same time may damage the DNA. Details are provided [10] elsewhere, a brief summary of which is given here in the Appendix.

INTRODUCTION

The UV from NPs damages DNA by ionizing radiation or produces ROS that damage the DNA by chemical reaction. In contrast, traditional biology focuses on how the DNA damage by ROS is transferred by chemical reaction across cellular tissue, body fluids, and membrane walls. The source of ROS is not defined in traditional biology.

PURPOSE

The purpose of this paper is to propose QED induced EM radiation in NPs as the mechanism which creates low-level UV radiation that:

- forms ROS and by chemical reaction damages the DNA,
- penetrates cellular membranes to damage the DNA by ionization,
- provides ROS that upon oxidative corrosion of CoCr NPs produces the Co ions that damage the DNA by entering the nucleus, and
- forms an EM potential for neurons to signal the central nervous system (CNS) that DNA has occurred.

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.DISCUSSION

Recently, QED induced radiation and the oxidative stress paradigm have been questioned [12] by DNA damage thought caused by signaling damaged DNA across multi-layers of BeWo cells. The NPs of CoCr were 30 nm in diameter while the barrier cells were grown on a 0.4 micron pore polyester filter supported on a Transwell insert, the insert positioned about 1 mm above the human fibroblast cells. Test conditions were (1) direct, (2) indirect, and (3) insert. DNA damage in direct tests occurs with the NPs in contact with the fibroblast; indirect DNA damage occurs with the NPs placed on top of the BeWo cells with the Transwell insert positioned above the fibroblast cells; and the insert test where the NPs are placed on the filter without the BeWo cells. Fibroblast DNA damage for the indirect test is claimed [12] greater than that for the insert test without BeWo cells, thereby suggesting the BeWo cells contributed to the DNA damage.

But the difference in DNA damage between indirect and insert tests is not significant, and in fact is about the same as that for the direct test. See (Fig. 1c of [12]). What this means is the 30 nm NPs or corrosion products of Co and Cr ions are passing through the BeWo cells and the 0.4 micron filter pores to enter the nucleus of the fibroblast cells. Perhaps, a thin nanoscale film instead of a porous filter would block the ions from the fibroblasts, thereby allowing the indirect effect of NP exposure to be tested with confidence.

In this regard, larger 2.9 micron sized CoCr particles that cannot pass through the 0.4 micron pores were also tested and shown [12] to produce comparable DNA damage to that found for the 30 nm NPs. Similarity is found with the greater DNA damage [8] by PM 2.3-10 than for PM < 2.5 particulate in air pollution studies. In the latter, the likelihood of < 100 nm carbon and silicate NPs in the sample allowed the argument that the coarse PM enhanced the DNA damage from the NPs. But this is unlikely for the CoCr NPs because the 2.9 micron CoCr particles were selectively processed to avoid NPs < 100 nm in the sample.

It is more likely the CoCr particles in fibroblast cells have a different DNA damage mechanism from the carbon and silica NPs embodied [1-7] in the production of ROS in the oxidative stress paradigm. Unlike NPs found in the air, CoCr particles in solution corrode into Co and Cr ions evidenced by the fact the Co ions are found in the nuclei of the fibroblast cells and not the CoCr particles themselves. Similar findings were reported in the companion study [13] of CoCr joint implants.

In contrast, carbon and silica NPs do not dissolve and are found in the cell nuclei as NP entities. Moreover, the DNA damage from Co and Cr ions for insert and indirect tests (Fig. 1c of [12]) is comparable to that for CoCr NPs and 2.9 micron particles. Cobalt has been long recognized [14] as genotoxic and carcinogenic. DNA damage by CoCr NPs is therefore more likely caused by the the toxicity of the Co ions and not the NPs and micron particles themselves.

.However, the DNA damage mechanism given by the corrosion of CoCr NPs into ions cannot be construed as a signaling mechanism through the BeWo barrier cells, but simply the diffusion of Co and Cr ions through the barrier cells and the filter pores to the fibroblast cells.

The reduction in indirect DNA damage by the CoCr NPs found upon adding drugs to the BeWo cells is claimed [12] caused by the suppression of cell-to-cell communication in the junctions between cells. However, this is unlikely. The drugs included: apyrase an enzyme hydrolyzing ATP; allopurinol that inhibits xanthine oxidase; and connexin and pannexin channel blockers, all of which are UV absorptive evidenced by the fact they are detected in liquid chromatography [15] by UV spectroscopy. What this means is the drugs are absorbing the QED induced radiation from the NPs, thereby reducing the corrosion of the CoCr NPs into Co and Cr ions and subsequent DNA damage from Co ions.

Moreover, the fact the corrosion of CoCr NPs explains the DNA damage without invoking cell-to-cell communication means the NPs are indeed producing EM radiation at UV levels and beyond. Perhaps, the choice of non-corrosive NPs would resolve whether the drugs are actually blocking the transfer of Co ions between cells or absorbing QED induced radiation.

EXTENSIONS

DNA damage by CoCr NPs across the BeWo barrier cells is related to both bystander effects and light activated neurons.

Bystander Effect

Radiation biology has traditionally considered damaged DNA as a source of EM radiation. Indeed, DNA damage to neonatal mouse cerebellum has been reported [16] *in vivo* in unexposed bystander cells, the mechanism of which is thought to be cell-to-cell communication of a signal from DNA damaged cells. DNA double-strand breaks and apoptotic cell death were thought induced in signals along bystander cerebellum cells by gap-junction intercellular communication in the CNS.

The DNA damage across the multi-layered barrier cells [12] differs from the bystander effect where neurons are activated throughout the CNS of the mouse. QED induced radiation may penetrate short distances across cellular barriers, but not the distance corresponding to the body of the mouse. Traditional biology lacks EM radiation from NPs to propagate beyond local DNA damage. In contrast, QED radiations are EM and produce an EM potential signal that can propagate throughout the CNS.

Light Activated Neurons

The electrical conduction of stimuli in nerve cells is an active area in brain research. Usually, a sharp metal electrode is inserted into the brain to introduce a current. But the attendant damage to tissue causes electrochemical side reactions. An alternative approach [17] uses micropipette coated with lead-selenide NPs. In rat brain slices, IR light is

used to create an electrical field from the NPs on the pipette surface. The pipette can then be moved around to stimulate neurons allowing the activation of regions of the brain having damaged or cut nerves to be restored without the need for disturbing wires.

Light activated neurons by NPs is consistent with QED induced EM radiation. However, the NP coated pipette is not needed. Instead, NPs attached directly to the neuron produce an EM potential allowing electrons to propagate through the CNS. Even light is not necessary. Indeed, water molecule collisions with NPs in the interstitial water between cells should produce a steady EM potential without the need for wires.

CONCLUSIONS

- QED induced radiation in CoCr NPs emits a low-level source of continuous EM radiation in the UV and beyond to produce ROS of peroxides and hydroxyl radicals from water that provides the source of damage to the DNA.

- By oxidation, the ROS corrode the CoCr NPs to form Co and Cr ions that damage the DNA by entering the nucleus.

- Drugs thought to reduce NP damage of DNA by blocking cell-to-cell communication are in fact reducing DNA damage by absorbing the UV from QED induced radiation.

- The EM potential that accompanies the QED induced radiation from NPs activates signaling, thereby informing the CNS that DNA damage has occurred.

- Traditional biology that assumes the NPs damage DNA by chemical reaction with ROS needs to be revised to include QED induced EM radiation as the source of the ROS..

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APPENDIX

The NP conserving collision energy of water molecules by the QED induced emission of UV radiation is shown in Fig. 1. In Fig. 2, NPs that that enter the biological cell are depicted to produce hydroxyl radicals that by ionization damage the DNA. But NPs external to the cell produce UV radiation that readily penetrates the membrane wall to damages the DNA.

Quantum mechanics precludes any temperature increase in the NPs upon molecular collisions. Fig. 3 giving the Einstein-Hopf relation for the harmonic oscillator at 300 K shows the heat capacity of NP atoms vanishes at EM confinement wavelengths $\lambda < 5$ micron. For spherical solid NPs of diameter D and refractive index n_r, the wavelength is, $\lambda = 2Dn_r$. Fig. 4 gives the dimensionless Einstein specific heat, $C^* = c_p/3Nk$, where c_p is the specific heat, N is the number of atoms, and k is Boltzmann's constant. Consistent with the heat capacity, C^* at $\lambda < 5$ micron also vanishes. For NPs < 100 nm, the wavelength < 1 micron and the specific heat is far less than that at 5 microns. Power Q_c absorbed from collisions of water molecules is shown in Fig. 5. For silver NPs, Fig. 6 shows the power Q_C is conserved by QED induced Planck energy E_P and photon rates dN_P/dt depending on the NP diameter D. The power Q_C for NPs < 100 nm is < 0.2 μW is upper bound by about $4x10^{11}$ photons having Planck energy E_P of 4.6 eV.

QED induced EM radiation requires fine D < 100 nm NPs to damage the DNA consistent with the oxidative stress paradigm. Coarse NPs emit QED induced NIR and lower radiation that does not damage the DNA, but enhances the UV from nearby fine NPs, thereby explaining experiments showing coarse NPs produce more DNA damage than fine NPs. Fig. 7 shows coarse NP emitting QED induced NIR which enhances that from the FIR by the ratio R > 1 as shown in Fig. 8.

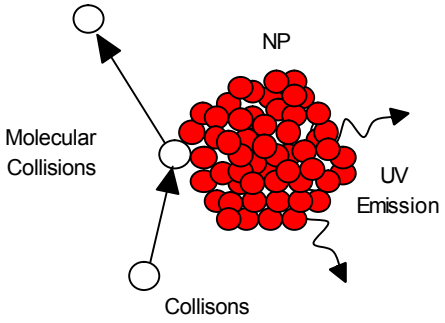

Fig. 1 NP conserving collision energy by emission of EM radiation

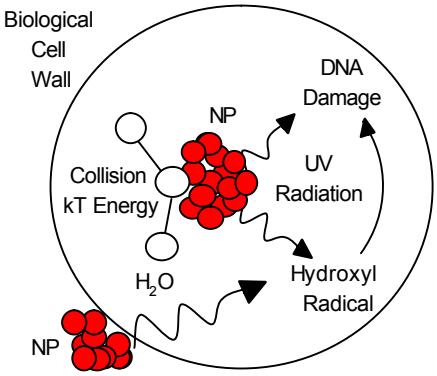

Fig. 2 DNA damage in Biological cell

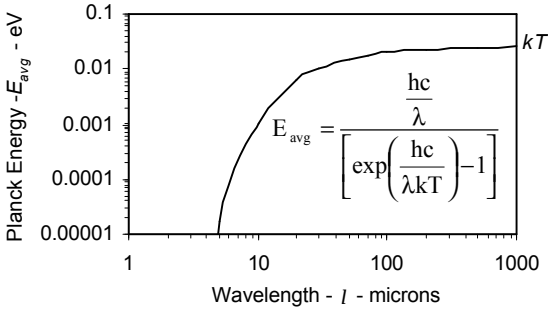

Fig. 3 Harmonic Oscillator at 300 K

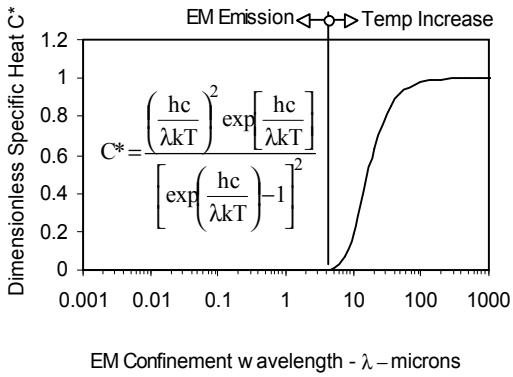

Fig. 4 Vanishing NP Specific Heat

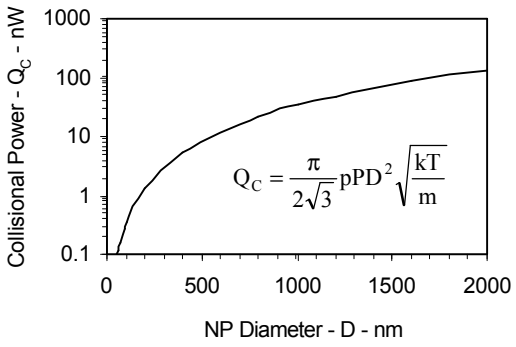

Fig. 5 Collision power in NPs

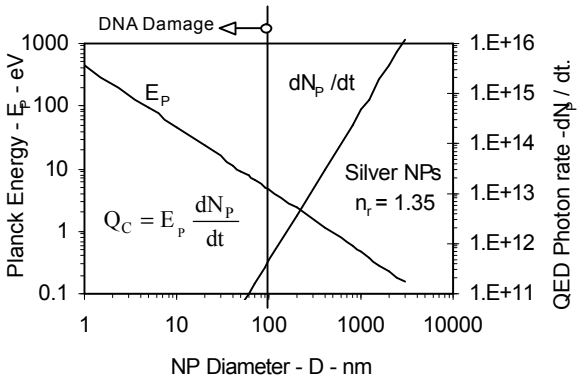

Fig. 6 QED radiation in silver NPs

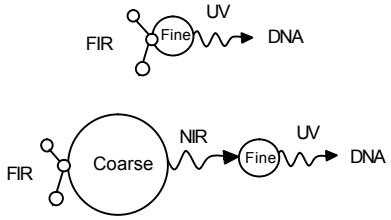

Fig. 7 Interaction of Coarse and Fine NPs

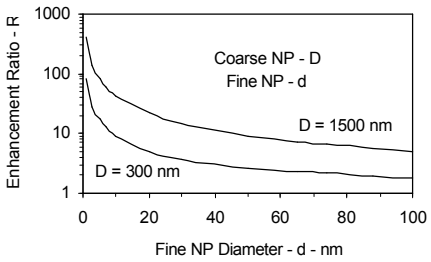

Fig 8 .Coarse NP Enhancement of Fine NPs