Nanoparticles and Cancer

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Abstract: Nanotechnology has over the past few decades claimed nanoparticles (NPs) destroy cancer cells. Recent research shows NPs also enhance the spread of cancer cells by increasing the gap between blood vessel epithelial cells allowing cancer cells by metastasis to leak into the bloodstream and spread throughout the body. However, if the mechanism by which the NP destroys the cancer cells is also the same as causing the cancer to spread throughout the body, any benefits of NPs in future medicine must be questioned. In this regard, simple QED shows NPs emit UV radiation that both destroys cancer cells as well as disrupting epithelial cells. Moreover, the UV damages and mutates DNA, the consequence of which may lead to decades later cancer. Simple QED is the consequence of the Planck law that denies atoms in NPs the heat capacity to conserve heat by an increase in temperature, and therefore conservation proceeds by NPs creating size-dependent standing EM radiation within and across the NP diameter. Because NPs have high surface-to-volume ratios, heat is deposited in the NP surface, the surface heat itself providing the brief EM confinement necessary for conversion into standing EUV radiation that after transfer to water fluoresces down to UV levels. NPs migrating into the gaps between epithelial cells emit UV thereby photo-charging gap surfaces producing electrostatic repulsion that widens the gap to micron levels allowing cancer cells to cross blood vessel walls and spread through the body. For 20 nm titanium dioxide NPs, EUV at ~ 20 eV is created that in water is lowered by fluorescence to UVC levels that do indeed destroy cancer tumors, but also disrupt vessel walls leading to the spread of the very cancer the NPs were intended to destroy.

INTRODUCTION

Over the past few decades, nanotechnology has promoted the paradigm that NPs provide health benefits by destroying cancer cells. Research showing NPs cause health problems [1] was not generally accepted as funding NP research would vanish. Similarly, recent cancer research [2] questioned the validity of the always positive benefits of NPs. Indeed, NPs were found to enhance the spread of cancer by increasing the gap between blood vessel epithelial cells allowing cancer cells to move into the blood stream and spread to other organs. Of concern is whether the mechanism by which the NP destroys the growth tumor is also the same causing the tumor to spread throughout the body.

If so, the paradigm of always beneficial NPs in nanomedicine must be reconsidered.

In cancer, endothelial cells are important as metastasis of tumors accounts for the vast majority of cancer mortality. The vascular endothelial monolayer forms a permeability barrier on the inner vessel wall to block cancer tumors from entering the blood stream and allowing the cancer to spread throughout the body. Intravenously administrated NPs are known to spread by blood circulation into various organs. But the mechanism by which NPs in the blood stream translocate across the endothelium into the targeted sites is not clear. In this regard, iron NPs were shown [3] to produce ROS and increase vascular permeability in human HMEVC cells along the Akt/GSK-3β signaling pathway in mitochondria as shown in Fig. 1(a). However, it is not clear how NPs in mitochondria produce ROS in the Akt/GSK-3β signaling pathway to enhance cell permeability. Indeed, the literature is silent on ROS creation by NPs.

Avoiding the uncertainty of NP-induced ROS and complexity of the Akt/GSK-3β pathway, a study [4] of NP-induced endothelial leakiness (NanoEL) was performed of intravasation and extravasation of cancer cells through disrupted blood vessels. The study tested the premise if NPs kill cancer cells then NPs also induce vascular leakiness. NPs were found to bind to and disrupt VE-cadherin bonds between endothelial cells depending on a complex relation between NP size, density and charge. The NanoEL scheme is shown in Fig. 1(b).

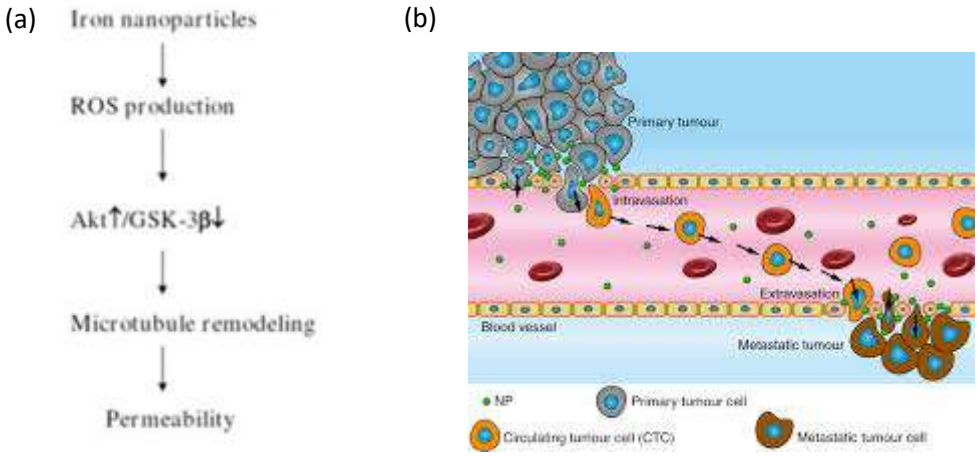

Figure 1. (a) Akt/GSK-3β pathway in iron NP cell permeability (b) NanoEL Schematic

The NanoEL study [4] used NPs of TiO_2, Au, Ag, and SiO_2 varying size from 18-23 nm, but was primarily based on 20 nmTiO_2 NPs. Fig. 1(b) shows NPs disrupting the endothelial wall allowing the primary tumor by intravasation enter the blood vessel and allow the circulating tumor cell (CTC) to translocate to another position. But NPs have also disrupted the downstream endothelial wall allowing the CTC to extravasate and spread to another location. NanoEL explains how cancer metastasis induced by NPs is initiated and continues by successive intravasation and extravasation.

PURPOSE

Vascular permeability in cancer metastasis is a complex process involving the coordinated regulation of multiple signaling pathways in the endothelial the cell. Indeed, the brief descriptions given here for metastatic cancer by the Akt/GSK-3β pathway and NanoEL are quite simplified. Moreover, many other theories of metastasis are omitted for brevity. Further, biological explanations of cancer metastasis include multiple paths the validity of which may never be known, especially in new areas of research such as NPs which lacks a theoretical basis itself. The need for a unifying theory of NPs in nanomedicine therefore seems to be more important than biological details. Hence,

The purpose of this paper is to propose NP-induced vascular permeability is caused by the NPs emitting EM radiation in the UV and beyond to the EUV. NP-induced UV is endogenous to the blood vessel. Biological parameters are assessed solely by exogenous UV experiments, thereby unifying cancer metastasis by the single variable of UV radiation.

ANALYSIS

Endogenous UV from NPs depends on simple QED - a method of analysis applicable [5] to nanoscale heat transfer. Simple QED is not the complex light and matter interaction advanced by Feynman and others. Instead, simple QED is readily understood by the Planck law of quantum mechanics that requires the heat capacity of constituent atoms in NPs to vanish under nanoscale EM confinement. In contrast, classical physics always assumes the atom has heat capacity and produces an increase in temperature upon the absorption of heat. Simple QED differs as the NP conserves heat by the creation of standing EM radiation inside and across the diameter d of the NP is illustrated in Fig. 2.

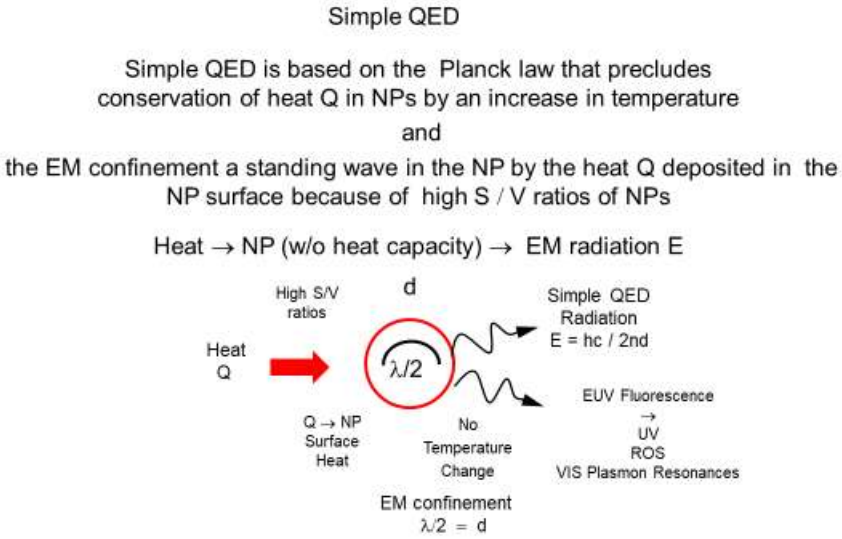

Figure 2. Simple QED conversion of heat to EM radiation

The heat Q into the NP is transferred from vessel blood or tissue as a thermal bath. Because NPs have high surface-to-volume ratios, the heat Q is almost totally absorbed in the NP surface. The NP temperature cannot conserve the surface heat Q by an increase in temperature, and instead a standing EM wave is created inside and across the diameter d of the NP having half-wavelength $\lambda/2 = d$. Correcting the velocity of light c for the refractive index n of the NP gives the time $\tau = 2d/(c/n)$ for 1 cycle. Hence, the wave frequency $c/\lambda = 1/\tau = c/2nd$ gives $\lambda = 2nd$.

Depending on NP size, simple QED creates standing EM waves from the UV to the EUV. For diameter $d < 50$ nm, the EM radiation is in the EUV while d near the upper limit of 100 nm produces UV and IR. The EM confinement to create the standing wave is the momentary surface heat of the NP. The EM radiation is emitted once the surface heat is dissipated in creating the EM standing wave. Typically, EUV waves excite lower quantum states by fluorescence, i.e., UV, ROS, and VIS plasmon resonances. For TiO_2 at UVC wavelengths, the refractive index $n \sim 3$. Fig. 3 shows simple QED radiation wavelengths $\lambda = 2nd$ produced for NP diameters $d < 100$ nm.

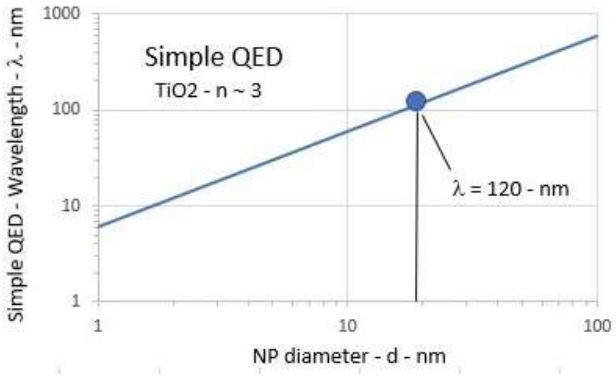

Figure 3. Simple QED wavelength v. NP diameter

The 20 nm NP having a simple QED wavelength $\lambda = 120$ nm is in the EUV at 10.35 eV and is representative of the EM emission [4] taking place in NanoEL using 18-23 nm NPs. Since the NPs are in contact with endothelial cells through water, the EUV is absorbed in water prior to exciting the endothelial cells. The EUV absorption [6] of water is shown in Fig. 4(a). However, the endothelial cells are absorbent is near the UVC [7] as shown for Keratin in Fig. 4(b).

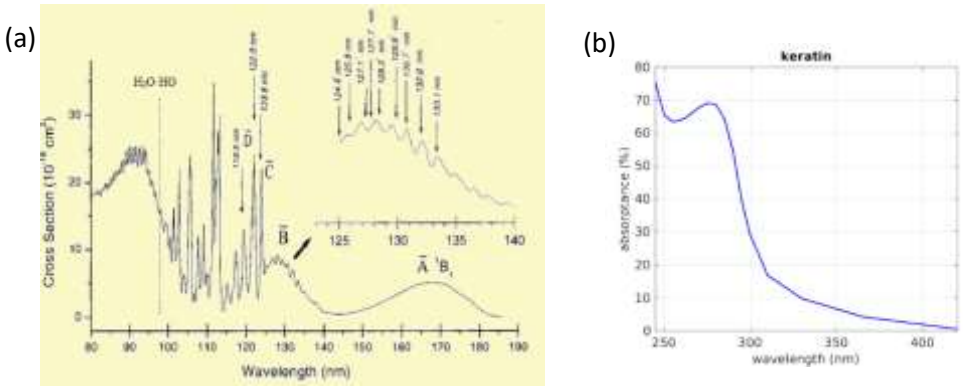

Figure 4. (a) EUV absorption water (b) UV absorption of Keratin

For NPs to excite endothelial cells, the EUV at 120 nm absorbed in water must fluoresce down to UV absorption levels, but data is scarce. In astronomy, the Lyman-α fluorescence [8] of water is fortunately available. Indeed, the Lyman-α photon having a wavelength 121.6 nm is virtually identical to the NP emission at 120 nm. However, fluorescence is inefficient. Fig. 5 shows conversion to 330 and 254 nm is about 8 and 13 percent a, respectively.

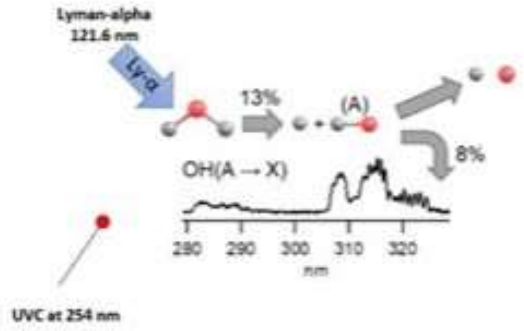

Figure 5. Fluorescence of water excited by the Lyman-α at 121.6 nm

The 20 nm NPs emits EUV at 120 nm, but the fluorescence efficiency in producing UVC at 254 nm is about 13 percent. Full 100 percent efficiency is achieved with larger NPs, e.g., 42 nm NPs produce UVC.

But what is the number of EUV photons created in the 20 nm NP?

In this regard, consider a spherical 20 nm NP in a blood or a water bath producing EUV from heat Q in the thermal surroundings as illustrated in in Fig. 6.

The Planck energy E of the 120 nm EUV photon is, $E = hc/\lambda = 1.66 \times 10^{-18}$ J. The NP is created from surface heat Q in time $\tau = 2d / (c/n)$. For a NP having refractive index $n \sim 3$, $\tau = 0.4$ fs. Hence, the heat $Q = E/\tau \sim 4$ mW. But the next EUV photon cannot be created until the NP surface temperature is recovered. Fourier's law valid only for atoms in blood having heat capacity kT is noted in the region R > Rs. The recovery of the initial temperature change ΔT taken from [9] depends on the thermal diffusivity α of blood, $\alpha = K_b/\rho C$, where K_b, ρ, and C are the thermal conductivity, density, and specific heat. Numerically, $\alpha = 1.24 \times 10^{-7}$ m^2/ s and $K_b = 0.52$ W /m-°K.

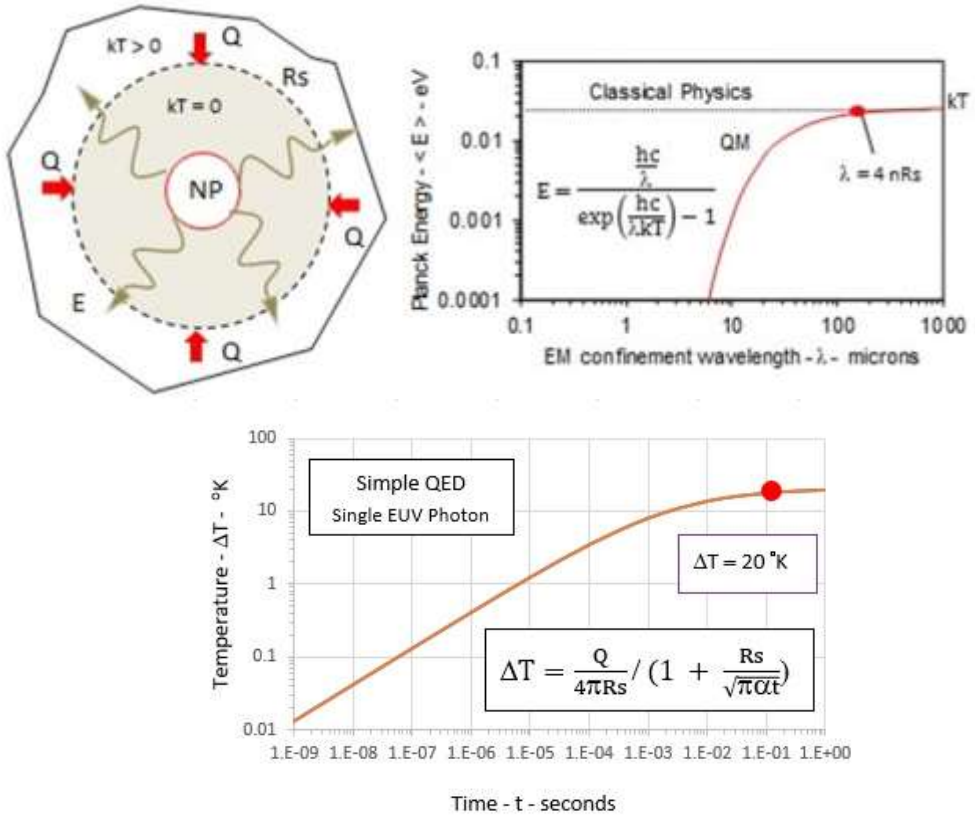

Figure 6. Recovery of NP surface temperature following single EUV emission

The Planck law at 300 °K shows atoms to have thermal kT energy at EM confinement wavelengths $\lambda > 200$ microns. The radius Rs at which blood atoms have thermal kT energy is noted. For blood having refractive index n = 1.6, the radius $Rs = \lambda/4n \sim 31$ microns. No temperature changes occur for $R < Rs$ including the NP. What this means is the heat flow Q from the bath for $R < Rs$ at temperature T is converted at Rs to EM radiation in the far IR and upon being absorbed at the NP surface produce the EUV photon. For a temperature change $\Delta T \sim 20$ K, the recovery time is about 0.1 s, or the single 20 nm NP produces about 10 EUV photons per second. But the 13 percent fluorescent efficiency from the EUV to the UVC gives ~ 1.3 UVC photons per second. Daily, the single 20 nm NP presents a significant burden on DNA repair as about 112,000 UVC photons are emitted to endothelial cells. Larger numbers of NPs increase the UVC levels proportionally.

DISCUSSION

A. UV Absorption Spectra and Vascular Leakage

The UV absorption spectra of biological tissue is important in assessing vascular leakage as without absorption chemical changes affecting leakage do not occur. Spectral data is obtained with UV sources exogenous to the vasculature. The major epidermal chromophores [10] comprising DOP Amelanin, urocanic acid, calf thymus DNA, tryptophane, tyrosine is shown in Fig. 7.

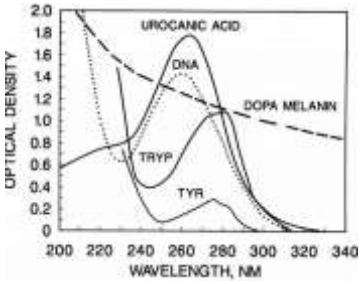

Figure 7. UV spectra of major epidermal chromophores.

The UV spectra show absorptions generally peak about UVC at 254 nm consistent with the UV absorption spectra of keratin shown in Fig. 4(b). The 20 nm NPs producing endogenous UVC in epithelial cells is expected to be absorbed. But does UV produce leakage?

In this regard, UVA < UVC is known [11] to cause abnormal leakage of macromolecules. The epidermis is composed mainly of keratinocytes in the skin with vascular VE-cadherin the major adhesion mediator between gap junctions in epidermal keratin. VE-cadherins are found [12] disrupted in UV irradiated HaCaT keratinocytes. Moreover, endothelin-1 (ET-1), a peptide that is secreted by keratinocytes [13] in response to UV irradiation is a potent down regulator of VE-cadherin in human melanocytes and melanoma cells. NP induced UV is therefore a cause of vascular leakage.

However, vascular leakage [14] in the endothelial cell may also be caused by ROS. As earlier described for iron NPs, ROS in the Akt/GSK-3β signaling pathway was thought [3] to enhance cell permeability. In this paper, exception is taken to the *ad hoc* creation of ROS to explain NP effects, i.e., ROS are not magically created in biological tissue, but require the EM energy at UV levels to react with water and oxygen to produce the OH hydroxyl and O superoxide radical. NPs provide the UV that down regulates VE-cadherin and creates ROS that cause vascular leakage. ROS is an intermediate to NP-induced UV deregulation of VE-cadherin. NP-induced UV is consistent with endogenous UV [15] produced in nanoscale mitochondrial features.

B. Catalase Pretreatment

Catalase is thought [3] to scavenge ROS and inhibit iron NP increases in HMVEC permeability. Again, the ROS intermediate is not necessary. Catalase is a UV absorber [16] as shown in Fig. 8.

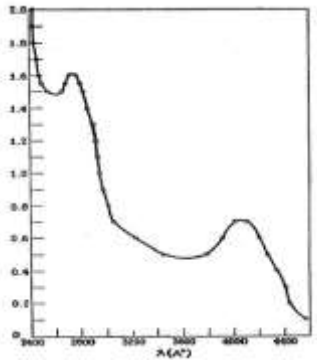

Figure 8. Catalase UV absorption spectra

Catalase pretreatment of HMVEC cells therefore absorbs the NP-induced UV to inhibit permeability. Explanations [3] of how catalase pretreatment blocked iron NP induced ROS in HMVEC cells avoids how iron NPs produce ROS, let alone how ROS enhance permeability.

C. Intrinsic ROS

To exclude the possibility that iron NPs may generate ROS intrinsically, cell free systems (cell culture media without HMVECs) were found [3] unable to produce ROS. However, supporting data is not presented. By simple QED, NPs are required to conserve heat by creating UV that produces the ROS. Data supporting the claims [3] that ROS are not created should be provided.

Indeed, the publication [3] should be retracted as a correction. Specifically, the statements:

> "These results demonstrate that iron nanoparticle-induced ROS production in HMVECs is generated from the cell oxidative stress response."
>
> "These results demonstrate that iron nanoparticle-induced ROS production in HMVECs is generated from the cell oxidative stress response."

should be deleted, the latter because simple QED was shown [15] to produce UV in mitochondria.

D. NanoEL Methodology

Cancer metastasis is a process in which cells from a tumor spread to other locations in the body. Usually, metastasis occurs through the bloodstream by intravasation and extravasation of endothelial blood vessels. NP induced endothelial leakiness (NanoEL) is a method (4,17-19) which NPs induce endothelial cells to separate allowing cancer cells in the blood stream to enter and leave the blood vessel as illustrated in Fig. 1(b). NanoEL is thought (4) to disrupt endothelial cell interactions by NPs binding to VE-cadherin depending on NP size, density, and charge. The disruption leaves micron sized gaps between adjacent cells by which cancer cells can translocate in and out of blood vessels.

However, the NPs need not bind to VE-cadherin. Simple QED requires the NPs create UV to conserve heat. The NP-induced UV disrupts VE-cadherins [12] in HaCaT keratinocytes and induces endothelin-1 (ET-1) to be secreted by keratinocytes [13] both of which are down regulators of VE-cadherin in human melanocytes and melanoma cells. NP-induced UV and not binding is the mechanism underlying metastasis by vascular leakage.

Certainly, cancer metastasis by NPs is to be avoided. But NPs are used throughout nanomedicine especially in treating cancer tumors prompting the question as to whether NPs should be used at all. Today, the dilemma in the widespread use of NPs in nanomedicine is the consequence of ignoring what nanotechnology knew over a few decades ago.

E. Simple QED Disruptive Force

The NanoEL disruptive force between adjacent epithelial cells is mediated by E–cadherin interactions. The gap g between cellular outer membranes is at least 22.5 nm. In [4,17-19] the NPs were 18-23 nm TiO_2, 10 - 30 - 50 nm Au, and 21 nm TiO_2, respectively. In NanoEL, the NPs migrate into the gap to bind to disrupt VE–cadherin interactions. NanoEL is based on complex chemistry, vessel disruption occurring by the phosphorylation of VE-cadherin, destabilizing actin, and leads to actin remodeling. The cell retracts and leakiness occurs. NanoEL may result in a loss of VE–cadherin near the cell membrane with the NP remaining bound to VE–cadherin.

However, NP-induced UV by simple QED avoids complex NanoEL chemistry with a more physical explanation of the disruptive force as shown in Fig. 9.

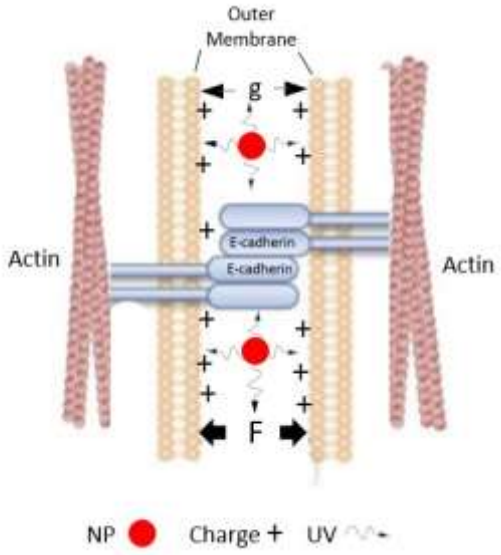

Figure 9. Simple QED - Disruptive Force

Like NanoEL, the NPs migrate into the gap g > 22.5 nm. But here simple QED differs from NanoEL in that the NPs emit UV to deregulate VE-cadherin, but also by the photoelectric effect charges the outer membranes of adjacent cells. UV at UVC levels removes electrons from the outer membrane atoms to induce a positive + charge for each electron removed. Recombination is negligible as the open gap ends allow the electrons to escape into the bloodstream. A repulsive electrostatic force F develops tending to open the gap g. For N electrons of unit charge e removed from a gap surface, remaining positive charges across a gap g produce the repulsive force F,

$$F = \frac{(Ne)^2}{4\pi\varepsilon\varepsilon_o g^2}$$

In water ($\varepsilon = 80$) the number N of electron charges,

$$N = \sqrt{4\pi\varepsilon\varepsilon_o F}\left(\frac{g}{e}\right)$$

The disruptive force F depends on the number N of charges, but is not known. Estimates [20] on the scale of physiological level give F ~ 5 pN. For g = 1 micron, N ~ 1300. Both gap surfaces require 2600 charges. For the single 20 nm NP calculated above, the 1.3 UVC photons induced per second take about 33 minutes to produce 2600 charges. In comparison, the 18-23 nm TiO_2 NPs showed [17] cell leakage to take about 30 minutes.

The repulsive force F ~ 5 pN is only an assumption, but still is in agreement with experiment. The NP-induced UV not only produces Coulomb repulsion, but also deregulates VE-cadherin adhesion consistent with increased vascular permeability. Experimental verification of NP-induced UV charging is recommended.

CONCLUSIONS

NPs cannot conserve heat from thermal surroundings by an increase in temperature because the Planck law of quantum mechanics precludes the atoms in NPs from having heat capacity. Conservation proceeds by simple QED creating standing EM radiation within and across the NP diameter. The EM radiation is intrinsic to NPs and nanoscale features < 100 nm of all biological structures. In contrast, macroparticles > 100 nm conserve heat by an increase in temperature.

Simple QED provides NPs with a source of UV radiation > 5 eV to create ROS of OH hydroxyl radicals and O super-oxides from cellular water and oxygen. Biological reactions in mitochondria thought induced by ROS are in fact produced by UV emissions from nanoscale features in cristae of mitochondria.

Cancer metastasis induced by NP-induced widening of gaps between epithelial cells need not be explained by complex chemical reactions that can never been verified. NPs that migrate into the gap only need simple QED to produce UV radiation that by the photoelectric effect charge gap surfaces to produce an electrostatic repulsive force that widens the gap to micron size allowing cancer cells to enter and leave the blood stream. However, NP-induced UV also deregulates VE-cadherin adhesion.

NPs are not always beneficial in nanomedicine. Indeed, the NP-induced UV that destroys cancer tumors is the same mechanism that by metastasis spreads the very same tumor through the bloodstream to other organs in the body. NPs in nanomedicine should not be treated as always beneficial, but avoided for patients disposed to cancer.

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