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Mini Review

A Grain of Salt: Metallic and Metallic Oxide Nanoparticles as the New Antimicrobials

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Metallic and metallic oxide nanoparticles are being hailed by some as a powerful new weapon against multi-drug resistant bacteria [1]. Their effectiveness against both bacteria and viruses are due to their high surface-to-volume ratio and their unique chemical and physical properties. Clearly there is an urgent need for new approaches to control multidrug resistant bacteria. These organisms are rapidly becoming a crucial concern for modern agriculture and medicine. For example in 2013, methicillin-resistant *Staphylococcus aureus* (MRSA) killed more people in the USA than Human immunodeficiency virus (HIV-AIDS), hepatitis B, and tuberculosis combined.

Foodborne pathogens, such as *Listeria monocytogenes, Salmonella spp.* and *Escherichia coli* can also exhibit resistance to antibiotics and disinfectants [1,2]. In addition, noble metals, such as, silver have a long history as antimicrobial agents dating back at least to 1000 BCE. In modern times, nano silver, copper, and silica have been successfully used in a variety of settings as both antimicrobial and anti-insecticidal compounds. Nanosilver is now being widely used in food packaging materials and also being proposed for use in surgical gowns and surgical gauze [3,4].

Silver nanoparticles (AgNPs) have been shown to be protective agents against numerous species of bacteria, including *E. coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, and several others [5]. Other metallic and metallic oxide nanoparticles have also been employed against bacteria including titanium oxide (TiO_2), magnesium oxide (MgO), copper (Cu), copper oxide (CuO), zinc oxide (ZnO), cadmium selenium (CdSe) and cadmium telluride (CdTe), [5].

The antimicrobial activity of silver has been established to be due to the release of Ag+ ions. This is evidenced in a number of studies going back to at least the 1970's. For example, one study utilized silver electrodes with weak direct current to inhibit growth on agar plates for the bacterial varieties of *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa* [6].These results are particularly interesting in that the strains used in this study were isolated from patients in the Veterans Administration Hospital in Syracuse, NY. Strains living in hospitals have been exposed to a number of biocidals and in general should be "tougher" than strains living in the general environment. Indeed, silver-resistant bacteria have been repeatedly found in burn wards, clinical and natural environments, and on human teeth [7]. While the exact mechanisms of silver nanoparticle toxicity to bacteria are not fully known, there is a growing consensus concerning the candidate actions. First, the action of silver nanoparticles occurs both by the release of silver ion (Ag+) as well as from potential disruption or damage to the cell wall and membrane caused by the particles themselves [1,7,8]. Silver interacts with the thiol group compounds found in respiratory enzymes of bacterial cells. It also binds to the bacterial cell wall and cell membrane inhibiting the respiration process [8,9]. Silver is known to act on *E. coli* by inhibiting the uptake of phosphorous and releasing phosphate, mannitol, succinate, proline, and glutamine from the cells [1,10]. The penetration of silver ions inside the cell is thought to impact the ability of DNA to replicate by causing it to condense. Furthermore, silver ions may interact with the thiol groups of proteins inside the cell causing these to become inactivated [1,11,12]. Due to the large surface area to volume ratio, smaller AgNPs should be able to more effectively release Ag+ ions into the cell and, following attachment to the cell membrane, may also penetrate into the cell [1,7,13-16]. Once inside, Ag+ ions may be lethal as they disrupt metabolism, cell signaling, DNA replication, transcription, translation, and cell division, either directly or through the generation of reactive oxygen species (ROS) [1,7]. It is the fact that metallic/metallic oxides impact so many aspects of bacterial physiology and reproduction that present thinking suggests that it will be difficult for bacteria to evolve resistance to them [1].

Numerous studies have now shown that the toxicity of NPs upon bacteria appears dependent on particle compositions, shape, size, and concentration (for AgNPs concentrations of > 75 µg/ml usually ceases growth; [1].) We also know that bacteria respond differently to these variables. For example, it was found that *Pseudomonas putida* illustrated orders of magnitude higher

resistance to ZnO NPs than either *E. coli* or *B. subtilis* [17]. The authors pointed out that *P. putida* is known to be heavy-metal resistant, often being isolated from heavy metal contaminated soils [18,19]. *P. putida's* heavy metal resistance is evidence that bacteria routinely evolve this trait in the presence of toxic heavy metals, just as we predict that bacteria exposed to metallic/metallic oxide nanoparticles due to their application in the medical and food industries will rapidly evolve de-novo resistance (or acquire already existing heavy metal resistance elements.)

BACTERIAL RESISTANCE TO METAL TOXICITY

Given the knowledge we already have concerning bacterial evolution, it seems contradictory that researchers developing new applications of metallic/metallic oxides for bacterial control have not considered if and how quickly resistance to these nanomaterials will evolve. We already have the experience of the rapid bacterial evolution of resistance to traditional antibiotics [20,21]. Over forty years ago, *Streptococcus pneumoniae* was considered widely susceptible to penicillin and other β-lactam antibiotics. Shortly afterwards, resistance to these antibiotics was reported all over the world, such that by 1997 resistance rates exceeded 30—70% of isolates derived from patients [20]. In addition, it is not correct to believe that traditional antibiotics impacted a very limited number of systems in their bacterial targets. For example, β-lactams effected the action of β–lactamases which hydrolyzed the β-lactam ring, modified target cell wall biosynthetic enzymes, altered the influx system of the outer membrane, and impacted active efflux systems [20]. Thus, understanding the mechanisms of evolution we should expect that despite the fact that metallic/metallic oxides NPs impact a great number of bacterial systems that the evolution of resistance to them is already occurring in nature.

Evolution by the means of natural selection requires three things, variation, heredity, and struggle for existence. In the case of the evolution of resistance to traditional antibiotics, there is evidence that there was ample variation in resistance to these compounds existing in nature well before the anthropogenic increase in their production [22-25]. It was shown that micro genomes collected from 30,000 year old Beringian permafrost contained genetic elements conferring resistance to β-lactam, tetracycline, and glycopeptide variants [23]. Structure and function analysis of the VanA element (which confers resistance to vancomycin) shows similarity to modern VanA elements. It has also been reported antibiotic resistance in samples derived from the culturable microbiome of Lechuguilla Cave, New Mexico [24]. The sample was taken from a region of the cave that has been isolated for over 4 million years. They reported that, like surface microbes, these bacteria were highly resistant to antibiotics; some strains were resistant to 14 different commercially available antibiotics. Resistance was detected to a wide range of structurally different antibiotics including daptomycin, an antibiotic of last resort in the treatment of drug resistant Gram-positive pathogens. Similarly to traditional antibiotics we know that resistance to heavy metals and metallic oxides already exists in nature [26-30]. The long-term sustainability of metallic/metallic oxide treatments for bacteria may already be compromised by the fact that there has been co-selection for both antibiotic and heavy metal resistance in nature [29,20]. The bacterium *Raoutella planticola* (formerly described as *Klebsiella planticola*) isolated from surface waters of the Kizilirmak River in Turkey has been shown to resistant to 15 antibiotics: ampicillin, amoxicillin/clavulanic acid, aztreonam, erthyromycin, imipenem, oxacillin, pefloxacin, penicillin, piperacillin, piperacillin/tazobactam, rifampin, sulbactam/cefoperazone, ticarsillin, ticarsillin/clavulanic acid, and vancomycin. It is also resistant to 11 heavy metals, aluminum, barium, copper, iron, lead, lithium, manganese, nickel, silver, strontium, and tin (range 8 to 5,000 mg/L). This bacterium was originally described from soil and water samples, but now is an important cause of invasive human infections in hospitals (nosocomial).

Co-selection can occur by two genetic mechanisms, linkage and pleiotropy. In the case of linkage, genes that confer resistance to a traditional antibiotic as well as to heavy metals are located close to each other on a segment of DNA. The DNA segment can be either chromosomal or plasmid borne. It has been well known since the 1970's that heavy metal resistance plasmids are circulating in nature [26]. One such plasmid was isolated from *Salmonella typhimurium* in a silver mine that carried genes for resistance to silver nitrate ($AgNO_3$), chloramphenicol, and ampicillin [31]. The silver resistance plasmid (180 kb) belongs to the IncHI incompatibility group and confers resistance to silver, mercury, tellurium, as well as several antibiotics [7,32]. The region that confers silver resistance sil-CFBA (ORF105aa) PRSE comprises 9 genes, of which 8 are characterized primarily by homologies with other known heavy metal resistance determinants [33]. Indeed, homologues to the silAB(ORF96)CRS are found on the chromosomes of *E. coli* K12 and O157 [34]. In the case of the sil-CFBA(ORF105aa)PRSE plasmid we also observe pleiotropy at work. Pleiotropy occurs when a gene for one trait also impacts other traits. For example, the silver resistance gene silP is a P-type ATPase efflux pump that transports silver ions from the cytoplasm to the periplasm. It may also function to transport traditional antibiotic substances from the cytoplasm. Silfen codes a periplasmic protein that probably functions as a chaperone, which transports Ag+ from SilP to the SilCBA complex (again this can work on other undesirable substances as well; [35]).

The SilCBA complex forms a three-polypeptide membrane-potential dependent cation/proton antiporter system that spans the entire cell membrane and belongs to the heavy metal efflux-resistance nodulation cell division family (HME-RND) family of efflux pumps. The complex consisting of an efflux pump (SilA), an outer membrane factor (SilC), and a membrane fusion protein (SilB) pumps Ag+ from the periplasm to the exterior of the cell. The gene *ofr105* is located between *silA* and *silP*and putatively codes for an uncharacterized protein of 105 amino acids. The silRS gene transcriptionally controls the silCFBA(ORF105aa) P genes; SilS is a transmembrane histidine kinase and SilR is a response regulator. These proteins are homologous to other two-component regulatory systems of heavy metals. For example, the cusS gene encoded a histidine kinase that senses elevated levels of copper and silver in the periplasmic space of *E. coli*. CusS has 56% sequence similarity with SilS [36]. We currently have evidence that a mutation in cusS helps to confer AgNP resistance in laboratory evolved strains of *E. coli* K12 MG1655 [37].

Clinical isolates of silCFBA(orf105) and silRS genes are more conserved than silP and silE. The silE gene encodes a periplasmic protein and is located downstream of silRS. The silE gene is under the control of its own promoter, and is strongly induced in the presence of Ag+. The precise mechanism of SilE is not yet known, but one SilE molecule can bind up to 38 Ag+ ions. Therefore it is thought that SilE is the first line of defense by binding Ag+ at the cell surface before it enters the cytoplasm [38]. Other heavy metal resistance systems such as PcoE exist. PcoE is part of a large plasmid-borne pcoABCDRSE cluster that confers periplasmic copper resistance and acts as a "metal sponge." It can bind multiple Cu+ and Ag+ ions. Bioinformatic analysis (BLAST, Graves 2014 unpublished; [38]) shows that Pco Eis homologous to SilE (48% identity). Chromosomally-located elements which are homologous to the *sil* determinants have been found in all *E. coli* strains [34,35]. In our experiment to develop AgNP resistant *E. coli* MG1655 we chose this strain because it did not have any *sil* elements or plasmids [37]. Originally we thought that it was possible that our laboratory AgNP resistance selection had acted on a homologous chromosomal *sil*-like segment. However, our subsequent genomic analysis shows that in the main, that this is not true [37].

The *cusCFBARS* gene cluster is mainly involved in copper resistance, it has also been shown to confer a certain amount of silver resistance (deletion of *cusA* resulted in silver sensitivity, [35]). CusCFBARS comprises a tri-component HME-RND efflux system (cusCBA), a small periplasmic Cu+ and Ag+ binding protein (CusF), and two-component regulatory system (CusRS). It seems that CusA can efflux metal ions from both the periplasm and the cytoplasm and uses methionine amino acid pairs or clusters to export Cu+ and Ag+. It has been demonstrated that CusB and CusF were constitutively expressed in a silver resistant *E. coli* strain, isolated by step-wise selection of increasing concentrations of silver, while both were undetectable in the silver sensitive parent strain [39]. This again illustrates an example of pleiotropy, a gene resulting from selection for one stress Cu+ ion, providing resistance to another stress Ag+ ion.

In summary, heavy metal resistance has evolved in nature and we can now show that it can also be experimentally evolved in laboratory populations [37]. An extreme example is that of *Cupriavidus metallidurans* a bacterium which is specialized for metal resistance and is associated with industrial sites linked to mining, metallurgical, and chemical industries. It has also been isolated from space craft related environments, patients with cystic fibrosis, and as an agent of an invasive human infection. It is also being used to bio-remediate environments and to precipitate pure gold. *C. metallidurans* CH34 harbors resistance determinants for at least 20 different heavy metals. The *silDCBA* and *cusDCBAF* operons that encode proteins that belong to the HME-RND family of transporters are located on a genomic island present on pMOL30 and the chromid (a 2nd bacterial chromosome that has features of both the chromosome and a plasmid, [40,41].) The *cupRAC*operon that codes for a P-type ATPase is located on chromosome 1. Recent isolates of *C. metallidurans* isolates from the potable water systems of the International Space Station and from the air of Kennedy Space Center Hazardous Payload Servicing Facility indicate that each isolate harbors at least one megaplasmid [42]. The silCBA operon is located on one of the megaplasmids. Another extreme example is seen in *Delftia acidovorans* and *Bordetella petrii*, silBCA is located on an integrative conjugative element (ICE) belonging to the Tn4371 family. This family carries functional modules involved in conjugative transfer, integration, maintenance/stability, and accessory genes conferring a special phenotype to the host bacteria. Thus in many strains the silver – heavy metal resistance elements are located on mobile genetic elements, facilitating the spread of these traits throughout the population.

The previous discussion has also illustrated the other two criteria for the evolution by means of natural selection of heavy metal resistance; heredity (genetic elements responsible for heavy metal resistance inherited vertically as well as horizontally) and struggle for existence (bacteria with heavy metal resistance surviving and reproducing in metal contaminated environments at higher rates than those without.) It is unlikely that nanoparticles have contributed thus far to the natural evolution of heavy metal resistance in nature. Nano-sized metals/metallic oxides can be produced naturally, but it is likely that bacterial communities will experience exponential increases in exposure to nano-scale versions of these compounds due to projected increases in their use as intentional biocides [43], as well as due to incidental exposure [44-46]. Increasing amounts of metallic/metallic oxide nanoparticles are being used in consumer products. For example, nano-TiO_2 is produced on a large scale for applications in paints, cosmetics, sunscreens, photocatalysts and solar cells, as well as water purification devices [47,48]. The predicted concentration of nanoTiO_2 in European waters for 2009 was 20 ng/L and 4 mg/L. The concentration of this compound predicted for American soil, sludge, surface water, Sewage Treatment Plant (STP) effluent, STP sludge, and sediment were 0.53 µg/kg/year, 42.00 µg/kg/year, 0.002 µg/L/year; 1.75 µg/L/year; 137 mg/kg/year, and 53 µg/kg/year respectively in 2008 [49]. Similarly values for nano-Ag were calculated at 6.6 µg/kg/year, 526 µg/kg/year, 0.088 µg/L/year, 16.40 µg/L/year, 1.29 mg/kg/year, and 153 µg/kg/year. These data suggest [29] that effluent particularly from agriculture and aquaculture could be fertile grounds for naturally evolving metallic/metallic oxide resistant bacteria. For example, a recent study reported data that already suggests that the deployment of silver nanoparticles in a water filtration system is generating silver resistant bacterial strains [50]. In this experiment, activated sludge (containing bacteria) was pumped through a membrane bioreactor system (MBR.) Silver nanoparticles averaging 6nm were pumped in the MBR at a concentration of 0.10 mg/L for the duration of the experiment (61 days.) They showed that the abundance of silver resistance gene *sil*E increased 50-fold after 41 days of exposure to a bacterial community. They could not detect increases in other known silver resistance genes such as *sil*S and *sil*P. Finally, they noticed that while the frequency of *sil*E was still elevated compared to the beginning of their experiment it had decreased significantly by day 65. They had no interpretation for this, but this could be indicative of the bacterial community acquiring other forms of adaptation. For example, an earlier study demonstrated that the exopolysaccharides of the blue-green bacterium *Synechocystis spp.* played a protective role against TiO_2 nanoparticles [48]. They utilized a *Synechocystis* strain that lacked the eps-gene which encodes the exo polysaccharide layer. The eps negative mutants

were much more susceptible to nanoparticle damage caused by photo-activated TiO_2 nanoparticles. This result illustrates that bacteria may have a multiple set of adaptive trajectories to minimize damage from metallic/metallic oxide nanoparticles. Determining the character of and the evolvablity of these resistance trajectories is the primary aim of my current research. This work suggests that bacteria will respond rapidly to metallic/metallic oxide nanoparticles. For this reason it is crucial that we begin to study how both de-novo evolution and horizontal transfer of existing metallic/metallic oxide resistance elements will confer resistance to nanoparticles. Therefore without these studies it is premature to conclude that metallic and metallic oxide nanoparticles should be hailed as miracle weapons against multi-drug resistant bacteria. Indeed, we should expect that bacteria will rapidly loose susceptibility to them, just as they did to conventional antibiotics.

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REFERENCES

1. Rai MK, Deshmukh SD, Ingle AP, Gade AK. Silver nanoparticles: the powerful nanoweapon against multidrug-resistant bacteria. J Appl Microbiol. 2012; 112: 841-852.
2. Ammendolia MG, Iosi F, De Berardis B, Guccione G, Superti F, Conte MP, et al. Listeria monocytogenes behaviour in presence of non-UV-irradiated titanium dioxide nanoparticles. PLoS One. 2014; 9: e84986.
3. Li Y, Leung P, Yao L, Song QW, Newton E. Antimicrobial effect of surgical masks coated with nanoparticles. J Hosp Infect. 2006; 62: 58-63.
4. Siqueira MC, Coelho GF, de Moura MR, Bresolin JD, Hubinger SZ, Marconcini JM, et al. Evaluation of antimicrobial activity of silver nanoparticles for carboxymethylcellulose film applications in food packaging. J Nanosci Nanotechnol. 2014; 14: 5512-5517.
5. Duncan TV. Applications of nanotechnology in food packaging and food safety: barrier materials, antimicrobials and sensors. J Colloid Interface Sci. 2011; 363: 1-24.
6. Spadaro JA, Berger TJ, Barranco SD, Chapin SE, Becker RO. Antibacterial effects of silver electrodes with weak direct current. Antimicrob Agents Chemother. 1974; 6: 637-642.
7. Mijnendonckx K, Leys N, Mahillon J, Silver S, Van Houdt R. Antimicrobial silver: uses, toxicity and potential for resistance. Biometals. 2013; 26: 609-621.
8. Rai M, Yadav A, Gade A . Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv. 2009; 27: 76-83.
9. Klasen HJ. A historical review of the use of silver in the treatment of burns. Part I early uses, Burns 2000; 30: 1-9.
10. Yamanaka M, Hara K, Kudo J. Bactericidal actions of a silver ion solution on Escherichia coli, studied by energy-filtering transmission electron microscopy and proteomic analysis. Appl Environ Microbiol. 2005; 71: 7589-7593.
11. Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO. A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. J Biomed Mater Res. 2000; 52: 662-668.
12. Liau SY, Read DC, Pugh WJ, Furr JR, Russell AD. Interaction of silver nitrate with readily identifiable groups: relationship to the antibacterial action of silver ions. Lett Appl Microbiol. 1997; 25: 279-283.
13. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, et al. The bactericidal effect of silver nanoparticles. Nanotechnology. 2005; 16: 2346-2353.
14. Panacek A, Kvítek L, Prucek R, Kolar M, Vecerova R, Pizúrova N, et al. Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity. J Phys Chem B. 2006; 110: 16248-16253.
15. Pal S, Tak YK, Song JM. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli. Appl Environ Microbiol. 2007; 73: 1712-1720.
16. Shahverdi AR, Fakhimi A, Shahverdi HR, Minaian S. Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphyloccoccus aureus and Escherichia coli, Nanomedicine, Nanotechnology, Biology, and Medicine. 2007; 3: 168-171.
17. Li M, Pokhrel S, Jin X, Mädler L, Damoiseaux R, Hoek EM. Stability, bioavailability, and bacterial toxicity of ZnO and iron-doped ZnO nanoparticles in aquatic media. Environ Sci Technol. 2011; 45: 755-761.
18. Guiné V, Spadini L, Sarret G, Muris M, Delolme C, Gaudet JP, et al. Zinc sorption to three gram-negative bacteria: combined titration, modeling, and EXAFS study. Environ Sci Technol. 2006; 40: 1806-1813.
19. Chen X, Wu W, Shi J, Xu X, Wang H, Chen Y. Adsorption of copper and zinc on Pseudomonas putida CZ1: particle concentration effect and adsorption reversibility. Colloids Surf B Biointerfaces. 2007; 54: 46-52.
20. Baquero F, Blázquez J. Evolution of antibiotic resistance. Trends Ecol Evol. 1997; 12: 482-487.
21. Levin BR, Perrot V, Walker N. Compensatory mutations, antibiotic resistance and the population genetics of adaptive evolution in bacteria. Genetics. 2000; 154: 985-997.
22. Mazel D, Davies J. Antibiotic resistance in microbes. Cell Mol Life Sci. 1999; 56: 742-754.
23. DCosta VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. Nature. 2011; 477: 457-461.
24. Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. PLoS One. 2012; 7: e34953.
25. Wright GD, Poinar H. Antibiotic resistance is ancient: implications for drug discovery. Trends Microbiology. 2012; 20: 157-159.
26. Silver S, Misra TK. Plasmid-mediated heavy metal resistances. Annu Rev Microbiol. 1988; 42: 717-743.
27. Silver S, Phung le T. A bacterial view of the periodic table: genes and proteins for toxic inorganic ions. J Ind Microbiol Biotechnol. 2005; 32: 587-605.
28. Shakibiae MR, Khosravan A, Zare AF. Application of metal resistant bacteria by mutational enhancement technique for bioremediation of copper and zinc from industrial wastes, Iran J. Environ. Health Sci. Eng. 2008; 5: 252-256
29. Seiler C, Berendonk TU. Heavy metal driven co-selection of antibiotic

resistance in soil and water bodies impacted by agriculture and aquaculture. Front Microbiol. 2012; 3: 399.

30. Koc S, Kabatas B, Icgen B. Multidrug and heavy metal-resistant Raoultella planticola isolated from surface water. Bull Environ Contam Toxicol. 2013; 91: 177-183.

31. McHugh GL, Moellering RC, Hopkins CC, Swartz MN. Salmonella typhimurium resistant to silver nitrate, chloramphenicol, and ampicillin. Lancet. 1975; 1: 235-240.

32. Gupta A, Matsui K, Lo JF, Silver S. Molecular basis for resistance to silver cations in Salmonella. Nat Med. 1999; 5: 183-188.

33. Silver S, Phung LT, Silver G. Silver as biocides in burn and wound dressings and bacterial resistance to silver compounds, J. Ind. Microbiol. Biotechnol. 33: 627--634, 2006.

34. Gupta A, Phung LT, Taylor DE, Silver S. Diversity of silver resistance genes in IncH incompatibility group plasmids. See comment in PubMed Commons below Microbiology. 2001; 147: 3393-3402.

35. Franke S. Microbiology of the toxic noble metal silver, in: Nies, D. and Silver, S. (eds), Molecular Biology of Heavy Metals. Microbiology Monographs, (Berlin: Springer), 2007.

36. Gudipaty SA, McEvoy MM. The histidine kinase CusS senses silver ions through direct binding by its sensor domain. Biochim Biophys Acta. 2014; 1844: 1656-1661.

37. Graves JL, Tajkarimi M, Iyer D, Tarannum M, Cunningham Q, Sharpe I, et al. Evolution of silver nanoparticle resistance in Escherichia coli, (in prep), 2014.

38. Silver S. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. FEMS Microbiol Rev. 2003; 27: 341-353.

39. Lok CN, Ho CM, Chen R, Tam PK, Chiu JF, Che CM. Proteomic identification of the Cus system as a major determinant of constitutive Escherichia coli silver resistance of chromosomal origin. Proteome Res. 2008; 7: 2351-2356.

40. Janssen PJ, Van Houdt R, Moors H, Monsieurs P, Morin N, Michaux A, et al. The complete genome sequence of Cupriavidus metallidurans strain CH34, a master survivalist in harsh and anthropogenic environments. PLoS One. 2010; 5: e10433.

41. Harrison PW, Lower RP, Kim NK, Young JP. Introducing the bacterial 'chromid': not a chromosome, not a plasmid. Trends Microbiol. 2010; 18: 141-148.

42. Leys N, Baatout S, Rosier C, Dams A, Heeren SC, Wattiez R, et al. The response of Cupriavidus metallidurans CH34 to spaceflight in the international space station. Antonie Van Leeuwenhoek. 2009; 96: 227-245.

43. Lara HH, Garza-Treviño EN, Ixtepan-Turrent L, Singh DK. Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds. J Nanobiotechnology. 2011; 9: 30.

44. Aitken RJ, Chaudhry MQ, Boxall AB, Hull M. Manufacture and use of nanomaterials: current status in the UK and global trends. Occup Med (Lond). 2006; 56: 300-306.

45. Nowack B, Bucheli TD. Occurrence, behavior and effects of nanoparticles in the environment. Environ Pollut. 2007; 150: 5-22.

46. Dobias J, Bernier-Latmani R. Silver release from silver nanoparticles in natural waters. Environ Sci Technol. 2013; 47: 4140-4146.

47. Mu L, Sprando RL. Application of nanotechnology in cosmetics. Pharm Res. 2010; 27: 1746-1749.

48. Planchon M, Jittawuttipoka T, Cassier-Chauvat C, Guyot F, Gelabert A, Benedetti MF, et al. Exopolysaccharides protect Synechocystis against the deleterious effects of titanium dioxide nanoparticles in natural and artificial waters. J Colloid Interface Sci. 2013; 405: 35-43.

49. Gottschalk F, Sonderer T, Scholz RW, Nowack B. Modeled environmental concentrations of engineered nanomaterials (TiO_2, ZnO, Ag, CNT, Fullerenes) for different regions, Environ. Sci. Technol. 2009; 43: 9216-9222.

50. Zhang C, Liang Z, Hu Z. Bacterial response to a continuous long-term exposure of silver nanoparticles at sub-ppm silver concentrations in a membrane bioreactor activated sludge system. Water Res. 2014; 50: 350-358.

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