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Review Article

Nanobiotics: Challenging the anti-microbial perspective - The game changer?

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Abstract: Antibiotics are the most important medical inventions in human history and are the invaluable weapons to fight against various infectious diseases. Multi drug resistant microorganisms are becoming a serious issue and increasingly public health problem in present day scenario. Antibiotics are becoming less useful due to increasing bacterial resistance. Development of new and more powerful antibiotics leading to drastic pathogens response by developing resistance to the point where the most powerful drugs in our arsenal are no longer effective against them. Newer strategies for the management of bacterial diseases are urgently needed and nanomaterials can be a very promising approach. Nanobiotics uses nano-sized tools for the successful management bacterial diseases and to gain increased understanding of the complex underlying patho-physiology of disease. (European Science Foundation. Forward Look Nanomedicine: An EMRC Consensus Opinion 2005. Available online: http://www.esf.org (accessed on 15 July 2017). The application of nanotechnologies to medicine, or nanomedicine, which has already demonstrated its tremendous impact on the pharmaceutical and biotechnology industries, is rapidly becoming a major driving force behind ongoing changes in the antimicrobial field. Present review providing important insights on nanobiotics, and their preparation, mechanism of action, as well as perspectives on the opportunities and challenges in nanobiotics.

Keywords: Nanobiotics, bacterial resistance, antibiotics

Introduction

Bacterial are tiny forms of life that can only be seen with a microscope. Millions of bacteria normally live on the skin, in the intestines, and on the genitalia. The vast majority of bacteria do not cause disease, and many bacteria are actually helpful and even necessary for good health. These bacteria are sometimes referred to as "good bacteria" or "healthy bacteria." Harmful bacteria that cause bacterial infections and disease are called pathogenic bacteria. Bacterial diseases occur when pathogenic bacteria get into the body and begin to reproduce and crowd out healthy bacteria, or to grow in tissues that are normally sterile. Harmful bacteria may also emit toxins that damage the body. Bacterial diseases are contagious and can result in many serious or life-threatening complications, such as blood poisoning (bacteremia), kidney failure, and toxic shock syndrome. Bacterial infection increases vascular permeability, which makes passive targeting possible. At the infection sites, the release and accumulation of bacterial components such as bacterial protease and lipopolysaccharide from gram-negative bacteria or lipoteichoic acid from gram-positive bacteria are known to trigger various inflammatory mediators that directly stimulate vascular permeability.

Antibiotic is a compound that decreases the growth of bacteria and are powerful medicines that fight against certain infections and can save lives when used properly by different mechanisms like; 1) inhibiting the cell wall synthesis; 2) stopping the folic acid synthesis; 3) blocking DNA/RNA expression; 4) disrupting cell membrane permeability and arresting the central dogma of bacteria (DNA, RNA and protein synthesis); 5) inhibiting the protein synthesis (http://en.wikipedia.org/wiki/Antibacterial). In the past 70 years, antibiotics have played major role in the management of infectious diseases caused by bacteria and other microbes. Antimicrobial chemotherapy has been a leading cause for the dramatic rise of average life expectancy in the 20th century. There is concern worldwide that antibiotics are being overused. This overuse is contributing toward the growing number of bacterial infections that are becoming resistant to antibacterial medications. Drug-resistant bacteria are emerging pathogens whose resistance profiles present a major challenge for containing their spread and their impact on human health (Witte, W; International dissemination of antibiotic resistant strains of bacterial pathogens. Infect.

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Genet. E2004,4, 187–191). Antimicrobial resistance is one of the major threats to human health.

Antimicrobial resistance is a complex mechanism whose etiology depends on the individual, the bacterial strains and resistance mechanisms that are developed (Andersson and Hughes 2010). Resistance genes have recently emerged favoured by improper use of antibiotics (D'Costa, *et al.,* 2011; Dos Santos, *et al.,* 2014). As the use of antibiotics increases for medical, veterinary and agricultural purposes, the increasing emergence of antibiotic-resistant strains of pathogenic bacteria is an unwelcome consequence. The incidence of the multidrug resistance (MDR) of bacteria which cause infections in hospitals/intensive care units is increasing, and finding microorganisms insensitive to more than 10 different antibiotics is not unusual (S-J. Chen, 2012).

Nanobiotics as antibacterials complementary to antibiotics are highly promising and are gaining large interest as they might fill the gaps where antibiotics frequently fail. Nanoparticles are in relation to biomedicine appeared in the late 1970s and are now the subject of over 10,000 publications per year, the term "Nanomedicine" only appeared at the turn of this century, and less than 30 papers including this term were published up to 2005. Nanoparticles are being viewed as elementary building blocks of nanotechnology, nanoparticles are now considered a viable alternative to antibiotics and seem to have a high potential to solve the problem of the emergence of bacterial multidrug resistance (Rai, *et al.,* 2012). Nanoparticles have been extensively explored to overcome the instability, undesirable systemic bio distribution, and toxicity frequently associated with the administration of soluble molecules (Tan ML, 2010.). It has been reported that conjugation of antigens to nanoparticle surfaces facilitated B-cell activation. (Villa C.H., 2011), due to a higher quantity of antigens that were delivered to antigen presenting cells (APCs) (Nembrini C., 2011).

Nanoparticle, or "nanobiotic", a small "interfering" piece of RNA (siRNA). They are a class of molecules designed to shut down specific genes. These scraps of genetic code seek out their mirror image within cells, such as bacteria, and silence them. This stops protein production and leads to cell death. Antimicrobial NM now in use (i.e., metal, metal oxide, and organic nanoparticles) show a diversity of intrinsic and modified chemical composition properties. Thus, it is not surprising that they have numerous modes of action (Figure 1).

Metals and metal oxides have been widely studied for their antimicrobial activities [Loomba L, 2013]. Metal oxide nanoparticles, well known for their highly potent antibacterial effect, include silver (Ag), iron oxide (Fe_3O_4), titanium oxide (TiO_2), copper oxide (CuO), and zinc oxide (ZnO). Silver nanoparticles have been widely used as an effective antimicrobial agent against bacteria, fungi, and viruses [Rai M, 2009]. Their effect was recognized already in ancient times.

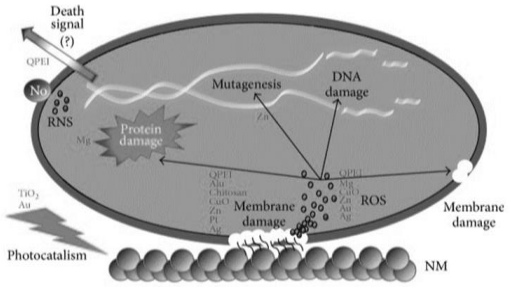

Figure: Nanobiotics mode of action.

Ag and its compounds have long been used for the disinfection. Ag compounds are commonly applied to treat burns, wounds, and a variety of infectious diseases [Avalos A., 2014; Aditya N.P., 2013]. The antimicrobial efficacy of Ag, as of other metals and metal oxide nanoparticles, was reported to be size-dependent [Poulose S, 2014]. Although the Ag nanoparticle mechanism of action is still not clear, small diameter Ag nanoparticles have a superior antimicrobial effect to those of a larger diameter [Panacek A, 2006]. Silver was reported to be an efficient bactericidal antibacterial agent against various pathogens *in vitro* and *in vivo* [De Simone S, 2014].

Titanium dioxide (TiO_2) is another metal oxide that has been extensively studied for its antimicrobial activities [Allahverdiyev AM, 2011]. TiO_2 has long been known for its ability to kill both Gram-positive and Gram-negative bacteria [Wei C, 1994]. TiO_2 is effective against many bacteria including spores of *Bacillus* [Hamal DB, 2010], which is the most resistant organism known. As with other NM, combinations of Ti or TiO_2 with other NM such as Ag were found to have a synergistic effect and to enhance their activity [Pratap Reddy M, 2007].

ZnO nanoparticles were shown to have a wide range of antimicrobial activity against various microorganisms, which is significantly dependent on the chosen concentration and particle size [Palanikumar L., 2014]. Moreover, ZnO nanoparticles were shown to inhibit the growth of methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and methicillin-resistant *S. epidermidis* (MRSE) strains and proved to be effective bactericidal agents that were not affected by the drug-resistant mechanisms of MRSA and MRSE [Malka E. 2013]. Zinc oxide (ZnO) NM are of relatively low cost and effective in size dependency against a wide range of bacteria [Huh, 2011].

Fe_3O_4 nanoparticles and gold (Au) represent an additional class of antimicrobial materials that are being researched for their use in health care [Chatterjee S., 2011]. Fe_3O_4 in its bulk form and Au are generally considered inert and lack antimicrobial properties. Interestingly, these materials can be modified to introduce antimicrobial properties when synthesized as nanosize particles. In comparison to Ag, gold- (Au) NM are less potent and have almost no antibacterial effect by themselves [Majdalawieh A., 2014].

Copper oxide (CuO) nanoparticles have been shown to be effective against various bacterial pathogens, their antibacterial efficacy is somewhat inferior to that of Ag or ZnO. Hence, a comparatively higher concentration of nanoparticles is needed to achieve the same results [Ren G., 2009]. Moreover, CuO nanoparticle activity varies greatly depending on the challenged bacterial species. Nonetheless, as Cu is much less expensive than other nanosized metal materials, it can be utilized for efficacy enhancement in the form of nanocomposites. Copper oxide (CuO) NM, like the other metallic nanoparticles, exert their antibacterial activity by membrane disruption and ROS production [Pelgrift R.Y., 2013]. Thus, it seems that in special cases it would be beneficial to use the CuO NM instead of others, including silver.

Nano-magnesium oxides (MgO) are additional antibacterial metal oxide NM that have been shown to exhibit bactericidal activity. Nano-MgO particles were reported to exhibit efficient antimicrobial activity against bacteria (both Gram-positive and Gram-negative), spores, and viruses. Compared to other metal nanoparticles, nano-MgO has the advantage that it can be prepared from available and economical precursors. In addition to inducing ROS, Mg-containing NM may directly inhibit essential enzymes of the bacteria [Blecher K., 2011]. MgF_2NM were found to prevent biofilm formation of *E. coli* and *S. aureus*.

Nitric oxide (NO) NM presents a promising antibacterial compound due to the low risk of possible resistance; that is, NO is involved in multiple mechanisms of antimicrobial activity [Carpenter A. W., 2012]. As other metal-based nanoparticles the antibacterial effect is dependent on size and shape; the smaller particles with a high aspect ratio are the most effective. NO is an endogenously produced molecule which is involved in various physiologic functions. Despite all its advantages, its clinical value is limited mainly because it is extremely reactive. However, NO's antimicrobial potential can be exploited upon its encapsulation, controlled release, and focal delivery [Kutner A. J., 2013].
Aluminum oxide (Al_2O_3) nanoparticles are suitable for antibacterial treatment. First, their bactericidal effect is relatively mild and they work only at high concentrations unless in combination with other NM such as Ag. Second and more disturbing is their ability to promote horizontal transfer of multiresistance genes mediated by plasmids across genera [Qiu Z., 2012]. The mechanism of action of aluminum NM, as recently shown for *E. coli*, is by diffusion and accumulation inside the cells, causing pit formation, perforation, and membrane disorganization, leading to cell death [Ansari M. A., 2014].

Organic Nanoparticles

Polymeric nanoparticles kill microorganisms either by releasing antibiotics, antimicrobial peptides, and antimicrobial agents or by contact-killing cationic surfaces such as quaternary ammonium compounds, alkyl pyridiniums, or quaternary phosphonium. Multiple mechanisms of action have been proposed for how these cationic groups are able to disrupt the bacterial cell membrane, with some requiring hydrophobic chains of certain lengths to penetrate and burst the bacterial membrane. It has been shown that high levels of positive charge are capable of conferring antimicrobial properties irrespective of hydrophobic chain length, perhaps by an ion exchange mechanism between the bacterial membrane and the charged surface. The antibacterial effect of polycations is dependent on the ability of multiple charges to attach to and interact with the cell membrane. These findings suggest the possibility of engineering a variety of polymer based positively charged surfaces to create a wide range of contact-killing materials [Lichter J. A., 2009]. Organic antibacterial materials are considered less stable in nature mainly at higher temperature when compared with inorganic materials. This may lead to difficulties that arise when designing products meant to be stable and able to withstand harsh process conditions.

Poly-ε-lysine is a cationic homopeptide of L-lysine which is effective against Gram-positive and Gram-negative bacteria. It also displays activity against spores of *B. coagulans, B. stearothermophilus*, and *B. subtilis* [Hiraki J. 1995].

Quaternary Ammonium Compounds

Quaternary ammonium compounds such as benzalkonium chloride, stearalkonium chloride, and cetrimonium chloride are well known disinfectants. Their antimicrobial activity is a function of the N-alkyl chain length and hence lipophilicity. Compounds with alkyl chain length 12–14 of alkyls provide optimum antibacterial activity against Gram-positive bacteria, while alkyls group with 14–16 carbon chains show better activity against Gram-negative bacteria. Initial interaction with bacterial wall results from electrostatic interaction between positively charged moieties of the

compound and negatively charged bacterial membranes, followed by the integration of the hydrophobic tail of the compound into the bacterial hydrophobic membrane core, where they denature structural proteins and enzymes.

Antimicrobial polymers with only one biocide end group on polymeric backbone were synthesized by cationic ring-opening polymerization of 2-alkyl-1,3-oxazolines, terminating the macromolecule with a cationic surfactant [Waschinski C. J., 2005]. Quaternary pyridiniums are compounds with a heterocyclic ring containing nitrogen atom. The antibacterial activity is a function of the pyridinium group in the polymer chain. Another family of antimicrobial polymer with aromatic/heterocyclic groups is imidazole derivatives.

Cationic Quaternary Polyelectrolytes are known cationic quaternary polyelectrolytes employed as antimicrobial polymers are acrylic or methacrylic derivatives, and a large number of them are synthesized from commercial methacrylic monomers such as 2-(dimethylamino)ethyl methacrylate. These polymers provide wide structural versatility by the alteration of hydrophobicity, molecular weight, surface charge, and other parameters [Muñoz-Bonilla A., 2012].

N-halamine compounds contain one or more nitrogen-halogen covalent bonds that are usually formed by halogenation of imide, amide, or amine groups, which provide stability and slow release free active halogen species into the environment. These oxidizing halogens promote the direct transfer of an active element to the biological target site or through dissociation to free halogen in aqueous media. These reactive free halogens lead to inhibition or inactivation of a microbial cell [Denyer S. P., 1998].

Preparation of Nanobiotics

Nano-antimicrobial materials can be synthesized by variety of different methods. Recent work showed that the mechanism of action and activity of materials may influence subsequent antimicrobial effect.

Titanium oxide (TiO_2) based nanofibers were prepared by electrospinning. Briefly, pluronic and PVP were each dissolved in ethanol. A TiO2 solution was prepared by adding titanium isopropoxide (TiP) in a mixture of ethanol and HCl. The solution was mixed with the PVP-pluronic solution followed by stirring at room temperature and the resulting precursor gel was heated at 50°C for 24 hrs. The gel was then electrospun and the formed fibers were calcined at 500°C for 4 hrs under air to form crystalline titanium dioxide nanofibers (Srisitthiratkul C., 2011).

Silver (Ag) compounds was introduced into a loading bath containing silver nitrate. To this solution CTAB and glucose were added and the mixture was shaken at 50°C. Subsequently, sodium hydroxide and water were added and the mixture was further shaken at 50°C. The coated samples were thoroughly rinsed with water and dried. The silver coated samples were washed with nonionic detergent (Triton X-100) and then the fabrics were dried (El-Shishtawy R. M., 2011).

Copper oxide nanoparticles were prepared by electrochemical reduction, using an electrolysis cell in which a copper metal sheet served as a sacrificial anode and a platinum (inert) sheet acted as a cathode. For this process tetrabutylammonium bromide in an organic medium acted as a structure-directing agent which was used with acetonitrile (ACN) at a 4 : 1 ratio. The reduction process was allowed to takes place under an inert atmosphere of nitrogen for 2 hrs. Desired particle size was achieved by controlling parameters such as density, solvent polarity, distance between electrodes, and concentration of stabilizers (Jadhav S., 2011).

Iron oxide (Fe_3O_4) & zinc oxide (ZnO) prepare the Fe oxide nanoparticles, $FeCl_2{\cdot}4H_2O$ solution was added to a porcine gelatine aqueous solution, followed by addition of a $NaNO_3$ solution and allowed to react for 10 min. Then the pH was raised to 9.5 by adding a NaOH aqueous solution (1 N). The Zn/Fe oxide composite nanoparticles were prepared similarly except for substituting the Fe^{2+} ions for a mixture of Fe^{2+} and Zn^{2+} of different weight ratios. The mixtures containing weight ratios [Zn]/[Fe] of 1: 9, 3: 7, 1: 1, 8: 2, and 9: 1 were prepared by mixing different volumes of $FeCl_2{\cdot}4H_2O$ solution with the appropriate volumes of $ZnCl_2$solution. The procedure that followed was as described for the iron oxide nanoparticles (Gordon T., 2011).

Magnesium oxide (MgO) prepared by microwave hydrothermal technique was used to prepare MgO nanowires. In brief, an aqueous solution of a fixed concentration of urea was added dropwise to an aqueous magnesium acetate solution. The solution was then loaded into a microwave furnace. The product obtained was collected, dried, and calcined to obtain a white-colored final material. (Al-Hazmi F., 2012).

Nitric oxide (NO) nanoparticles was synthesized by adding tetramethyl orthosilicate, polyethylene glycol, chitosan, glucose, and sodium nitrite in sodium phosphate buffer. In this glass composite, nitrite was reduced to NO due to redox reactions initiated with thermally generated electrons from glucose. After the redox reaction, the ingredients were combined and dried using a lyophilizer,

resulting in a fine powder consisting of nanoparticles containing NO. The water channels inside the particles of the hydrogel/glass composite opened in an aqueous environment, facilitating the release of the trapped NO over extended periods of time (Martinez L. R., 2009).

Polyethylenimine and quaternary ammonium compounds was prepared by ethanol solution of PEI was cross-linked with 8.7 mmol dibromopentane (PEI monomer/dibromopentane). The generated HBr was neutralized by treatment with sodium hydroxide and the resulting residue was purified from NaBr by gravitational filtration and dried under reduced pressure. The cross-linked PEI was further alkylated with bromooctane, as described above, to produce octane alkylated PEI. Octane alkylated PEI dispersed in anhydrous THF was reacted with methyl iodide in the presence of 2% cross-linked 4-vinylpyridine. The product was filtered to remove 4-vinylpyridinium salt and the filtrate was evaporated to dryness under reduced pressure (Beyth N., 2006).

Chitosan & polyguanidines prepared in HCl and then adjusted to pH 8-9 by 5% w/v aqueous sodium carbonate. The precipitate was washed with water and the desired amount of amino imino methane sulfonic acid was added. The reaction was kept at 50°C for 15 min and then the mixture was cooled to room temperature. Once cooled it was poured into saturated aqueous sodium sulfate, and the precipitate was filtered off, washed thoroughly with water and ethanol, and then dried under vacuum to give guanidinylated chitosan (Hu Y., 2007).

The biocompatibility of nanomaterials must be explored prior to their use in biomedical applications such as drug delivery, gene delivery, biosensors, or the treatment of wound infections. In such applications, the NM come in direct contact with tissues and cells, where they can cause beneficial or destructive effects on the body. The effect of NP on various body tissues is not known, and the interaction of NM with cells and tissues is poorly understood.

It has been suggested that nanobiotics mainly rely on very different mechanisms of antimicrobial activity when compared to antibiotics. The technology behind the nanomaterial synthesis is a key point to consider. Several techniques are available exploring reactions in solid state and reactions that involve chemical methods for wet-chemical synthesis such as: sol-gel, co-precipitation, polymeric precursor method, hydrothermal methods. These nanostructure particles can be of controllable size with large surface area in relation to their molecular weight. These features have led to different approaches (e.g. incorporating nanoparticles in solid materials or diffusing them into medicines) and many hypotheses about the mechanism of action have been proposed: a) Release of toxic ions (Cd2+, Zn2+, Ag+) that can bind to sulfur-containing proteins of the cell membrane and interfere in cell permeability; b) Toxic ions that can cause DNA damage; c) Interruption of electron transport, protein oxidation and membrane potential collapse due to its contact with CeO2 or nC60; d) Generation of ROS (Reactive Oxygen Species) that can cause disruption of cell membrane. These mechanisms may not operate separately suggesting that more than one mechanism can occur simultaneously. Another point to consider is the difference in effectiveness against some bacteria and fungi species. For instance, it is accepted that inhibitory activity of silver ions is higher for Gram negative bacteria than for Gram positive species of similar behavior. Several examples of nanomaterials with antimicrobial properties can be found in dentistry and medicine. These nanostructured particles are already present in restorative materials, in catheters and curatives. Fluorescent staining plus microscopic investigation and Zeta potentials are relevant techniques for evaluation of bacteria viability. It must be pointed out that nanotechnology is also available for other health applications such as biological markers for cancer treatments. Finally, the adverse effects of nanomaterials cannot be ruled out. Thus, more clinical trials as well as research in the level of molecular biology are needed for a safely use. Moreover, the production and synthesis of the nanomaterials have to consider the application of green nanotechnology principles assessing the environmental risks of manufactured nanomaterials. The application of nanotechnologies to medicine, or nanomedicine, which has already demonstrated its tremendous impact on the pharmaceutical and biotechnology industries, is rapidly becoming a major driving force behind ongoing changes in the antimicrobial field.

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