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EDITORIAL

From the magic bullet to nanotechnology: nanoantimicrobials as therapeutics to fight multidrug-resistant microorganisms

Desde la bala mágica a la nanotecnología: nanoantimicrobianos para combatir microorganismos multirresistentes

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A century ago, Paul Ehrlich, a Nobel laureate in 1907, defined the concept of ''magic bullet'' to propose selective drug targeting, aiming to deliver drugs to the right place, at the correct concentration, and for an appropriate duration, without harming the host organism. The global emergence and spread of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria have become a critical global healthcare concern, which is currently considered one of the principal threats by different global health organizations due to the limited efficacy of antimicrobial (ATM) agents[1]. MDR to first-line drugs increase healthcare costs and generate the need for effective and safe alternative treatments. However, the number of newly developed and approved ATM drugs has decreased over the past decades. The availability of few effective antimicrobials and the necessity to develop novel strategies and innovative antimicrobials emphasize the need for novel approaches and different safe and effective alternatives[2].

Nanotechnology is one of the most promising technologies of the 21st century, involving synthesis, engineering and systems with novel or enhanced properties. Nanomaterials (NMs) are nano-sized substances where at least 50% of the particles have one or more external dimensions ranging from 1 to 100 nanometers. Nanoparticles (NPs) are NMs with all three external dimensions in the nanoscale. NMs and NPs have emerged as a promising approach to fight against microbial infections and are postulated as having the potential for overcoming the limitations of current ATM drugs, with a reduced likelihood of developing resistance for action in various ways[3].

The use of NMs and NPs is among the most promising strategies to overcome the limitations of current ATM drugs. However, their mechanisms of action are poorly understood, with three main mechanisms of ATM effect that have been proposed[4,5]:

1. **Release of metal ions:** Metal NPs contain metal components, such as silver, copper, gold, and others, which can be gradually released into the surrounding environment, triggering the death of microbial pathogens through the interaction with biomolecules.
2. **Oxidative stress induction:** Metal ions induce intracellular oxidative stress disrupting the prooxidant-antioxidant balance, which can lead to irreversible cellular damage.
3. **Physical damage:** NMs and NPs can cause physical damage to microbial cells by disrupting the cell wall and interfering with the permeability of the cell membrane.

The combination of these mechanisms contributes to the ATM effects of NMs and NPs. Their ability to simultaneously target multiple cellular components and pathways can make it challenging for microorganisms to develop resistance. However, this outcome depends on the type of NMs

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and NPs, the microorganism involved, and the surrounding environment, among other factors[2,3].

Antimicrobial NMs and NPs can be classified, based on their properties, shapes or sizes, into inorganic-based NMs and their metal oxides, organic-based NMs, carbon-based NMs, and composite-based NMs[3]. Particularly, metal NPs are considered promising due to their tiny size, unique physicochemical properties, high chemical reactivity, ease of preparation and stability over time. The similar size to intra- and extra-cellular components allows specific interactions with microbial molecular and subcellular structures, such as the plasma membrane and macromolecules. Furthermore, their broad-spectrum activity makes them valuable candidates for several ATM applications. Metal oxide NPs (e.g., titanium dioxide, zinc oxide) possess photo-catalytic properties that can generate Reactive oxygen species (ROS) upon exposure to light. NPs, particularly silver and gold NPs, can inhibit biofilm formation or disrupt the biofilm matrix, altering its architecture with the reduction of persister cells. These actions depend on the pore sizes of the biofilm matrix, the charge of both NPs and matrix, the hydrophobicity of the surrounding environment, and the chemical gradient within the matrix. However, they exhibit problems of aggregation and accumulation affecting their stability and efficacy[4,5].

Organic-based NMs, including liposomes, polymeric micelles, polymeric NPs, and solid lipid NPs offer good compatibility as well as biodegradability, controlled drug release, and ease of functionalization for targeted delivery. These NPs are versatile carriers for ATM agents. However, there are challenges related to storage stability and controlled release that involve drug loss. Nanocellulose and nanostarch are derived from natural materials and have an interest for sustainable and eco-friendly approaches. Carbon-based NPs such as carbon nanotubes and graphene can be functionalized for ATM activity including ATM coatings and drug delivery. Composite-based NMs, which combine varied materials, can offer synergistic effects of traditional agents, thus enhancing overall ATM activity[3].

Examples and potential applications of nanomedicine in the field of ATM treatment include the utilization of NMs or NPs for various purposes[2,3]:

Nanocoatings for Medical Devices: Polymeric NMs have become more popular in recent years to create ATM nanocoatings on medical devices due to their high biocompatibility and biodegradability, which help prevent microbial adhesion and biofilm formation on the surface of the devices.

Nanoparticle Carriers for Drug Delivery: NMs and NPs can be engineered as drug carriers or delivery systems, such as liposomes and polymer carriers, to encapsulate ATM agents and deliver them directly to the infection site. This targeted drug delivery improves drug concentration, reducing systemic exposure and minimizing side effects on the host organism. Additionally, NPs can protect ATM drugs from degradation, increasing their stability and prolonging their shelf life.

Detection Systems for Microbial Diagnostics: Functionalized NPs can interact with specific microbial components, leading to detectable changes in measurable signals, facilitating the quick and accurate identification of infections.

NPs in Vaccines: a wide range of NPs, particularly liposomes, polymeric and inorganic NPs can be employed as vaccine carriers or vaccine adjuvants, improving antigen presentation and robust immunogenicity.

The history of nanoscience is relatively short, yet it has experienced exponential growth. However, there are still some voids concerning potential risks in future applications, exposures, and long-term effects regarding human health and the environment (such as, persistence in air, water, soil, and biological systems). Currently, the production of NMs and NPs has reached a substantial scale, with hundreds of thousands of tons being manufactured worldwide. An illustrative example of this growth is the production of AgNPs that has been estimated to increase from 360–450 tons per year to 800 tons by the year 2025[5]. Conversely, there are certain clinical limitations that raise concerns about cytotoxic effects, metabolism, clearance, activation of proinflammatory cytokines and chemokines, premature drug release, removal by phagocytes, and stability within the dynamic conditions within the human or animal body[3,4]. There are uncertainties surrounding the use of NMs (fue abrevado antes) in different applications, including nanomedicine, thereby highlighting the need for rigorous testing and thorough assessment of their safety profiles before clinical implementation[6].

In conclusion, the global spread of MDR, XDR, and PDR is a pressing concern, and NMs and NPs show great potential in offering the opportunity to exploit their unique qualities by manipulating their nanoscale properties. Nevertheless, the application of NMs and NPs as ATM agents is still in the initial stages of development and further investigation into their potential risks and challenges is essential to fully harness the power of nanotechnology. Therefore, the identification of the most promising NPs and the understanding of the interplay between NMs and NPs and microbial systems are necessary for future applications in the nanobiology and nanomedicine fields. There are still challenges to overcome, such as biocompatibility, potential toxicity, and strict regulatory approval processes. The development of effective nanoagents based on an exhaustive understanding of their mechanisms of action remains a crucial challenge in the battle against MDR microorganisms.

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