How can nanoparticles contribute to antituberculosis therapy?

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Therapeutic approaches using nanoparticles are being successfully used in foods and in several fields of medicine, including infectious diseases. Regarding tuberculosis (TB) treatment, nanoparticles can be a useful strategy for two distinct applications: (i) for their intrinsic antimycobacterial activity; (ii) as vehicles for known antitubercular drugs to allow reduction of dose- and drug-associated side-effects and administration via user-friendly administration routes such as pulmonary or oral ones. Promising results were obtained *in vitro* and in animal *Mycobacterium tuberculosis* models and need now to be translated into clinical drug candidates. Such a prospect can provide an opportunity regarding the current limited therapeutic options for drug-resistant TB and the scarcity of novel antituberculosis drugs in the drug discovery pipeline.

Introduction

The problem of antibiotic resistance in *Mycobacterium tuberculosis* has been declared a global health emergency by WHO that could endanger the control of tuberculosis (TB). Rising cases of multi-drug-resistant (MDR) TB and extensively drug-resistant (XDR) TB all over the world are increasingly hindering treatment of TB, making mandatory the use of second-line drugs (SLDs) [1]. Treatment of MDR-TB is expensive, prolonged (18–24 months) and complex (with at least a combination of five drugs that include some injectable drugs), and is associated with a higher incidence of adverse effects. New drugs are urgently needed but, despite the fact that several molecules are being investigated, some of them already in clinical trials, only bedaquiline and delamanid have been approved for conditional treatment of specific MDR-TB patients in the past years [2,3].

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It is obvious that, besides classical drug discovery strategies, new approaches are urgently needed to get a faster, more-efficient and less harmful treatment. For this purpose, nanoparticles (NPs) have been shown to be useful and versatile tools that can be used as antibacterial agents, and also as drug delivery systems, with numerous examples in the literature regarding various antibiotics and antibacterial agents. Nowadays, several groups across Europe (including universities, small and medium-sized enterprises, research institutes and pharmaceutical companies) join forces together in the frame of research consortiums to apply nanotechnology for the development and implementation of novel treatments for MDR pathogens, including MDR- and XDR-TB.

Use of NPs as new tools in TB treatment

NPs: characteristics and advantages for TB treatment

Very simply, we could consider a NP as a tiny object measuring less than 1000 nm that works as a whole unit (Fig. 1, [9]). They can be made of very different materials [biodegradable lipids, liposomes, solid-lipid NPs, polymers like poly lactic-co-glycolic acid (PLGA) or

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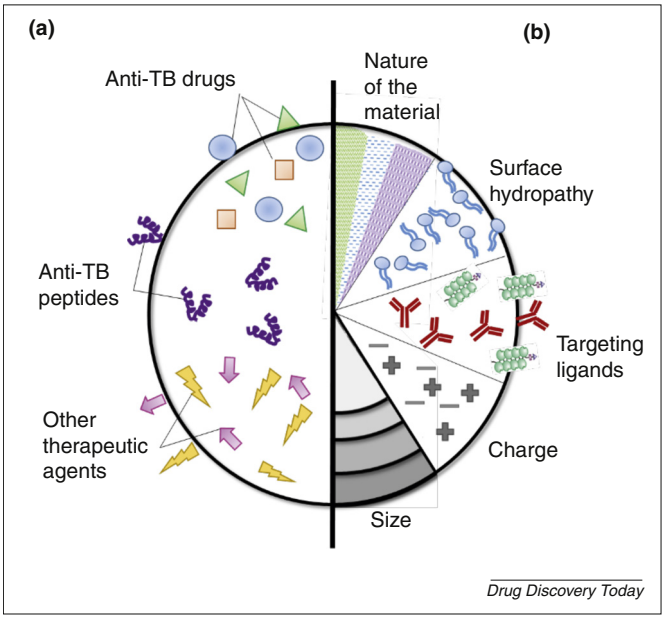

FIGURE 1

Composition and properties of nanoparticles. **(a)** Composition of the different types of nanoparticles that have been tested for activity against *Mycobacterium tuberculosis*, such as those encapsulating first- or second-line anti-TB drugs, alone or in combination, as well as other potentially useful particles such as antimicrobial peptides, other therapeutic agents or small DNA fragments. **(b)** The main nanoparticle properties that can influence the uptake, distribution and efficacy of nanoparticle-based therapies are: nature of the material, size, surface charge, surface hydropathy and targeting ligands.

Source: Adapted, with permission, from [9].

polysaccharides like chitosan], and can be produced by different methods, resulting in NPs with different structures and sizes.

NPs made of inorganic materials show antibacterial activity. The most common are the metal NPs (such as Ag, Au, Ga, Cu, etc.), which possess unique physical, chemical, electrical, optical, mechanical and magnetic properties, and their antimicrobial effects are well documented [4–8]. One second, and probably the major, advantage of nanocarriers is their use as drug delivery systems owing to their unique physicochemical properties. In general, they are of small size, high surface:volume ratio and high stability [9]. Normally they can incorporate lipophilic and hydrophilic drugs (Fig. 1, [9]), as well as other molecules such as carbohydrates, proteins or lipids to stabilize and functionalize them [6]. In this way, NPs can improve the aqueous solubility of poorly soluble drugs, protect the drugs from degradation and allow a controlled release of the loaded drug, thereby the dose and frequency of administration can be reduced. Additionally, they can be modified to control their biodistribution allowing selective delivery to target organs or tissues [9]. For all those characteristics NPs are smart tools for the improvement of pharmacokinetics, solubility, bioavailability, toxicity or pharmacodynamics of drugs.

The development of effective and safe nanotherapeutic methods is particularly relevant in the treatment of drug-resistant tuberculosis, because very long treatments with highly toxic second-line drugs are required for those cases. The properties of NPs could diminish the dose of the drugs used to treat MDR-TB, and direct them to the infected macrophages in the lung, decreasing the toxicity and side-effects, and increasing their efficacy. To this end, dedicated NPs must be developed for each TB drug and optimized for targeting the lungs harboring extracellular as well as intracellular bacteria.

NPs with intrinsic antimycobacterial activity

Metal NPs present antimicrobial activity against a variety of microorganisms, and *M. tuberculosis* is not an exception (Table 1). Silver (Ag) has been used as an antibacterial agent for centuries [10,11]. Its antimicrobial activity is reported to increase when in the nanoform, which could be as a result of its ability to enter through cell membranes [12], and nowadays silver NPs (AgNP) are widely used in consumer products such as textiles, disinfectant sprays, antibacterial ointments, bandages and medical devices [13]. AgNPs are reported to have high antibacterial properties against Gram-positive and Gram-negative bacteria [11,12,14–17]. Because of that, the specific antimycobacterial activity of AgNPs has been studied, and it has been reported that AgNPs show higher activity against mycobacteria than copper oxide NPs, followed by zinc oxide NPs, with poor antimycobacterial activity for both of them [13].

The synthesis of AgNPs can be done via chemical methods but also physical methods. Concerning the chemical methods, sodium citrate, sodium borohydride and dimethylformamide are typical compounds used to reduce Ag^+ into metallic silver [18]. However, as for organic NPs, ecofriendly pure methods based on the use of apiin, geraniol and gum kondagogu as reducing agents were also shown to be successful for producing AgNPs so that the synthesis process of AgNPs is not an impediment to their development [19]. A study showed that AgNPs synthesized by synthetic agents present greater bacterial inhibition [20], although AgNPs synthesized from medicinal-plant-derived reducing agents also present antimycobacterial activity [21]. In both studies, it was reported that the antimycobacterial activity of AgNPs is higher than that of gold NPs (AuNPs), and lower than the bimetallic ones (Au–Ag) despite the mechanism of action of each metal still being under investigation. Other strategies like combining the effect of biogenic-AgNPs and antimicrobial cationic peptides are being investigated [22], and are revealed as a promising antimycobacterial strategy.

Certain types of NPs, like any other antibiotic, can carry the risk of developing resistance. After exposure to AgNPs, *Mycobacterium smegmatis* populations resistant to AgNPs and $AgNO_3$ were obtained, and they were cross-resistant to antibiotics as well, although no cross-resistance was observed with other inorganic compounds like $CuSO_4$ and $ZnSO_4$ [23]. This suggests that general resistance mechanisms such as efflux pumps could be mediating resistance to these materials, which needs to be properly addressed. Besides their *in vitro* antibacterial properties, AgNPs have been reported to suppress innate responses of monocyte-derived macrophages in response to *M. tuberculosis* infection [24]. This ability of NPs to modulate pathogen-induced immune responses must be further taken into account when one wants to fully understand the impact of NPs in *in vivo* models of infection.

Gallium (Ga) is a metal very similar to iron (Fe), which is essential for the metabolism and growth of *M. tuberculosis*. Substituting Ga for Fe in the active site of enzymes can render them nonfunctional, and this is a potential approach for novel antituberculous therapy. Ga has been reported to present antimicrobial activity against mycobacteria [25], showing efficacy in murine