Bioinorganic functionalization to enhance the uptake of nanoparticles in Gram-negative bacterial cells.

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Antimicrobial resistance is a growing health concern associated with high mortality rates. Alongside the increased number of resistant bacterial strains identified and the reduced number of new antibiotics in the pipeline, the development of new antimicrobial therapies is crucial.[1] Silica nanoparticles present unique properties for the design of novel drug delivery systems for antibiotics that are unable to be internalized in Gram-negative bacterial cells. The chemical versatility of their surface and framework proposes an advantage for the design of innovative antibiotic delivery systems.[2,3]

Iron is one of the most important nutrients for bacterial-cells, as it is involved in a large variety of metabolic processes. Bacteria cells can obtain extracellular iron in different ways, by siderophore-based iron uptake is the most efficient strategy. Siderophores are natural Fe(III) chelators produced by bacterial cells with high Fe(III) affinity that after scavenging Fe(III) from the growing media are internalized through highly specific siderophore surface receptors.[4] Due to this unique properties, Siderophore-Antibiotic conjugates (SACs) have been widely explored to enhance the antibacterial activity of several antibiotics following the “Troyan horse” strategy.[5] Nevertheless, this approach has never been applied to nanoparticles.

Hence, to enhance the nanoparticle cell interactions and subsequent particle internalization, aminocarbocylate-based Fe(III) complexes that mimic natural siderophores were developed. Previously developed luminescent vancomycin-loaded silica nanoparticles[2] were *in situ* functionalized with the Fe(III) complexes (Figure 1). The particles displayed optimal luminescent properties for imaging and sustained antibiotic release. The particles displayed high antibacterial activity. Even lowering the minimal inhibitory concentration of vancomycin, a non-active antibiotic against Gram-negative bacterial cells, against a wide range of tested Gram-negative bacterial cells. Electron and structured illumination microscopy revealed high nanoparticle internalization in bacterial cells, compared with uncoated and Fe(III)-free coated particles. Upon overexpression of siderophore receptor, the activity and internalization of nanopartciles was increased, suggesting that these receptors are involved in the mechanism of action of the nanoparticles. Similarly, *S. aureus*, *E. coli* and *P. aeruginosa* strains with inactivated surface siderophore receptors were employed to identifies specially the involved receptors. The results depicted that the nanoparticles interact with specific carboxylate- and aminocarboxylate-based siderophore receptors, which facilitates the nanoparticle internalization.

These results represent the first example in the literature of a nanoparticle-based drug delivery system interacting with siderophore surface receptors, expanding the application of siderophore-conjugated from SACs. Furthermore, the enhanced nanoparticle internalization could be used to repurpose antibiotics that, currently, are not being employed due to their lack of penetration abilities in Gram-negative bacterial cells.

References

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Figures

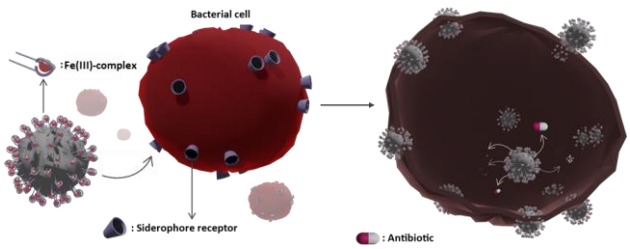

Figure 1. Scheme of the developed Fe(III)-aminocaboxylate coated silica nanoparticles.