Targeting mononuclear phagocytes for eradicating intracellular parasites

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Abstract

Mononuclear phagocytes such as monocytes, tissue-specific macrophages and dendritic cells are primary actors in both innate and adaptive immunity, as well as tissue homoeostasis.[1] They have key roles in a range of physiological and pathological processes, so any strategy targeting these cells will have wide-ranging impact. These phagocytes can be parasitized by intracellular bacteria, turning them from housekeepers to hiding places and favouring chronic and/or disseminated infection.[2] One of the most infamous is the bacteria that cause tuberculosis, which is the most pandemic and one of the deadliest diseases with one-third of the world's population infected, and 1.8 million deaths worldwide in 2015. Here we demonstrate the effective targeting and intracellular delivery of antibiotics to both circulating monocytes and resident macrophages, using pH sensitive nanoscopic polymersomes made of poly(2-(methacryloyloxy)ethyl phosphorylcholine)-co-poly(2-(di-isopropylamino)ethyl methacrylate) (PMPC-PDPA).[3] Polymersome selectivity to mononuclear phagocytes is demonstrated and ascribed to the polymerised phosphorylcholine motifs affinity toward scavenger receptors. Finally, we demonstrate the successful exploitation of this targeting for the effective eradication of intracellular bacteria that cause tuberculosis, Mycobacterium tuberculosis, as well as other intracellular parasites including the Mycobacterium bovis, Mycobacterium marinum, and the most common bacteria associated with antibiotic resistance, the Staphylococcus aureus.

Results

In this work, we have demonstrated that PMPC-PDPA polymersomes can be loaded with a large variety of antibiotics, including proteins (lysostaphin), small peptides (vancomycin), glycols (gentamicin), poorly water-soluble organics such as quinones (rifampicin) and functionalised pyridines (isoniazid), thus covering a large repertoire of possible chemistries. We have shown that polymersomes can deliver antibiotics to treat intracellular pathogen-related infections, and to potentially decrease the dose and duration of treatment required for bacterial eradication. Both in vitro (in human cells) and in vivo experiments demonstrated that these nanoscopic synthetic vesicles were specifically internalised by macrophages, without inducing toxicity, through a combination of dynamin-independent endocytosis and phagocytosis. We have demonstrated that drug-encapsulated polymersomes were able to reduce S. aureus, Bacille de Calmette-Guerin (BCG - M. bovis), M. tuberculosis, and M. marinum bacterial burden, again using in vitro and in vivo approaches. Antimicrobial-loaded polymersomes were more effective compared with the same concentration of free drug, and in some cases were able to eradicate the intracellular microorganisms completely. We thus believe this technology can be exploited to reduce the effective dose required for therapy, with a consequent potential reduction in antimicrobial resistance. In addition, encapsulation of antimicrobials could help completely eradicate infection from the host more rapidly, by direct delivery of drug to the immune system to enhance the host-pathogen response.

References