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Poster abstract submission

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Poster title

Makromolecular prodrug nanoparticles for the treatment of intracellular persisting pathogens

Poster abstract

Aspergillus fumigatus is the major causative of invasive aspergillosis in immunocompromised patients, a life-threatening disease with mortality rates up to 95%. After inhalation of its spores (conidia) by humans, they are facing alveolar macrophages as first line of immune defense in lungs. Like many other pathogens, A. fumigatus has evolved mechanisms to avoid its elimination inside phagolysosomes (PLs) of these cell type. The treatment of intracellular persisting pathogens is challenging, because the utilized drugs have to cross two membranes, the cytoplasmic and the PL membrane. This and the increasing number of resistant strains highlights the importance for the development of new approaches. Drug delivery systems bear the potential to reach intracellular persisting microorganisms and, by applying macromolecular prodrugs (MPDs), can lead to high local concentrations of the drug This helps to overcome resistance and also decreases the systemic concentration, leading to less side effects.
The aim was to elucidate, whether nanoparticles (NPs) can target intracellular persistent pathogens and if a drug release specifically in these intracellular organelles is possible. Dye-labeled NPs with a size large enough for phagocytosis by macrophages were formulated to track their internalization into RAW 264.7 macrophages by imaging flow cytometry. Intracellular localization was confirmed by fluorescence microscopy and TEM. The MPDs were consisting of an antifungal drug, a peptide linker specifically cleaved by enzymes in PLs and a polymer. Drug release from MPDs was quantified by LC-MS analysis. Macrophages internalized NPs efficiently and addition of NPs to prior infected macrophages confirmed co-localization of NPs and conidia in the same PL due to fusion of separate PLs. The number of phagolysosomes containing both conidia and NPs increased at elevated NP concentrations or after addition of the fusion enhancer Vacuolin-1. Dye-labeled MPD also showed co-localization with conidia in PLs and drug release was only occurring intracellularly.
In conclusion, the fusion of conidia- and NP-containing PLs was proven as mechanism for NPs reaching intracellular conidia and fusion rate could be increased by certain methods. Furthermore, smart prodrugs were employed to release the drug only in the PL. These results represent the requisite for the development of advanced delivery systems for the treatment of intracellular persistent pathogens.

Research topic

Small molecule therapeutics