pH-responsive NanoImmunoTherapy for Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by progressive synovial inflammation [1]. Current therapies include glucocorticoid and disease-modifying anti-rheumatic drugs [1]. Despite well-known immunosuppressive and anti-inflammatory activity, these drugs are associated with deleterious side effects. Mostly due to the limited selectivity, rapid clearance and widespread biodistribution into non-target tissues [1]. Macrophages and synoviocytes found within the synovium are responsible for the modulation of the synovial inflammatory response [1]. In this study, we present pH-responsive polymersomes made of poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) and poly(2-(diisopropylamino)ethyl methacrylate) (PDPA) diblock copolymer as suitable drug delivery nanocarriers able to target and effectively mediate the intracellular drug release along the endocytic pathway [2-3]. The cell selectivity is ascribed to the high targeting specificity of PMPC block to the scavenger receptor B type I [2-3]. Once inside the synovial cell, the PDPA block bestows the necessary pH trigger hence enabling drug's endosomal escape [2-3].

Polymersomes were characterized in terms of vesicle size, morphology and drug loading capacity. Additionally, drug release studies mimicking blood (pH 7.4), inflamed synovium (pH 6.5) and endosomes (pH 5.0) physiologic microenvironments were performed to evaluate polymersomes stability and pH responsiveness. The *in vitro* performance of drug loaded polymersomes in human macrophages and synoviocytes included live cell uptake kinetics and anti-inflammatory efficacy related to nuclear factor kappa B signaling transduction using confocal laser scanning microscopy. Additional cells response to the anti-inflammatory activity of drug loaded pH-responsive polymersomes was assessed by quantitative polymerase chain reaction and enzyme-linked immunosorbent assay. This approach takes advantage of the pH sensitivity, the selectivity and stability of pH-responsive polymersomes in order to increase the bioavailability of drug within target synovial cells. To this end, polymersomes have the therapeutic potential to enhance the drugs anti-inflammatory and immunosuppressive efficacy, while limiting well-known off-target side effects in chronic RA therapy.

References

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