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Diethylene glycol functionalized self-assembling peptide nanofibers and their hydrophobic drug delivery potential

Parisa Sadatmousavi [a], Tewodros Mamo [b], P. Chen [a,*]

[a] Department of Chemical Engineering, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1
[b] Nanotechnology Engineering, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

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ABSTRACT

Self-assembling peptide nanofibers have emerged as important nanobiomaterials, with such applications as delivery of therapeutic agents and vaccines, nanofabrication and biomineralization, tissue engineering and regenerative medicine. Recently a new class of self-assembling peptides has been introduced, which takes into consideration amino acid pairing (AAP) strategies in the peptide sequence design. Even though these peptides have shown promising potential in the design of novel functional biomaterials, they have a propensity to initiate uncontrollable aggregation and be degraded by proteolytic enzymes. These present the most significant challenge in advancing self-assembling peptides for in vitro and in vivo applications. Functionalizing biomaterials with polyethylene glycol (PEG) has been shown to surmount such problems. Here the results of conjugating diethylene glycol (DEG), a short segment of PEG, to one of the AAP peptides, AAP8, with eight amino acids in sequence, are reported. The results indicate that incorporation of DEG into the peptide sequence modulates fiber self-assembly through creating more aligned and uniform nanostructures. This is associated with increasing solubility, stability, and secondary structure β-sheet content of the peptide. The DEG conjugate of AAP8 also shows reduced cellular cytotoxicity. Functionalization of AAP8 improves the capability of the peptide to stabilize and deliver a hydrophobic anticancer compound, ellipticine, in aqueous solution, consequently inducing greater cytotoxicity to lung carcinoma cells over a relatively long time, compared with non-functionalized AAP8. The presented functionalized peptide and its drug delivery application indicate a potentially useful design strategy for novel self-assembling peptide biomaterials for biotechnology and nanomedicine.

1. Introduction

Self-assembling peptides are a class of biomaterials showing promising results for various biomedical applications, including delivery of therapeutic agents and vaccines, nanofabrication, biomineralization, tissue engineering, and regenerative medicine [1–3]. Recently a new class of self-assembling peptides based on the design principle amino acid pairing (AAP) has been introduced, with the model peptide AAP8 showing great promise in creating β-sheet-rich nanofibers, and stabilizing and delivering a hydrophobic anticancer agent [4]. The design of AAP self-assembling peptides is unique as it is based on the combination of several side-chain interactions, including hydrophobic interactions, electrostatic interactions, and hydrogen bonding. While these newly designed systems and other self-assembling peptides have shown immense potential, issues remain in optimizing the self-assembled structures and making them more robust for in vivo applications [5]. A major issue to be addressed in improving the self-assembled fibril nanostructure is avoiding uncontrollable aggregation of the β-sheet structures while improving the capability of the fibers to form predictable nanostructures [6,7]. The surface of the nanofibers must be modified for effective biomedical applications in vivo. Conjugating the peptide units with a short segment of polyethylene glycol (PEG) polymer is here proposed to address these issues.

Surface functionalization of nanoparticles (NPs) with PEG has become a standard strategy to increase the NP half-life in the bloodstream, as the functionalization reduces protein opsonization and macrophage uptake [5,8,9]. By reducing non-specific interactions with proteins through its hydrophilicity and steric repulsion effects, PEG results in long lasting circulating drug delivery systems with reduced opsonization and complement activation [5]. PEG has been approved by the US Food and Drug Administration (FDA) for clinical use due to its low toxicity and lack of immunogenicity. A number of clinically approved therapeutics rely on PEG for improved in vivo profiles, including liposomes (Doxil), PEG–drug conjugates (Oncaspar) and polymeric NPs (Genexol-PM) [10]. Various researchers have also shown an effect of PEGylationon iron oxide NPs for in vivo cancer imaging due to the enhanced permeability and retention

* Corresponding author. Tel.: +1 519 888 4567x35586; fax: +1 519 746 4979.
E-mail address: p4chen@uwaterloo.ca (P. Chen).

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