Repurposing Amyloid beta as drug delivery carrier through controlled nano-assembly

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Amyloid beta is an intrinsically disordered protein capable of self-assembling into highly ordered cross beta sheet fibrils implicated in neurodegenerative diseases. Due to their structural polymorphism, inherent biocompatibility and excellent self-assembly properties they are ideal for repurposing into therapeutic materials with minimal immunogenic risk. Protein nanoparticles have gained attention as next generation drug delivery vehicles for cancer treatment due to their multiple advantages such as biocompatibility, versatile functionalisation, biodegradability. However, the design of carriers often rely on complex, energy-intensive synthesis routes involving toxic solvents. In addition, the challenges in suitability of proteins to withstand carrier synthesis conditions limit their clinical translation. In this work, we demonstrate the repurposing of amyloid beta (Aβ) - as proof of concept, into a non-pathogenic and biocompatible nanocarrier for drug delivery application. Factors such as solvent environment, pH, and biopolymer interactions were identified as integral in redirecting the protein's aggregation pathway toward stable, amorphous nanostructures rather than toxic fibrils. These findings were integrated with the development of drying-induced self-assembly method which is a solvent-free, energy-efficient, and highly scalable production workflow for nanoparticle synthesis. Aβ was successfully repurposed into stable, drug loaded amyloid beta nanoparticles in the size range of 130-200 nm, with high encapsulation efficiency which demonstrated the feasibility of the developed synthesis technique. The Aβ NPs exhibit a slow diffusion-mediated drug release. In vitro studies on MCF-7 breast cancer cell lines demonstrated enhanced cytotoxicity and ex-ovo CAM assay revealed significant inhibition of tumour-induced angiogenesis and downregulation of pro-angiogenic markers VEGFA, FGF2, and ANG1. Through this research, we aim to demonstrate repurposed protein based therapeutic systems with promising translational potential.

Keywords:
Amyloid beta, cancer therapeutics, drug delivery