Self-Assembled Tannin Complexes for Redox Responsive Drug Delivery

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Introduction: Tannins are naturally occurring macromolecular polyphenols capable of associating with various biomolecules to form inter-polymer complexes (IPC). They also exhibit anti-inflammatory, oxidative, and microbial properties[1] that could be useful for biomedical applications. Of particular interest are the IPCs that they form with poly(ethylene glycol) (PEG). However, IPC studies are limited by purity and molecular weight of plant extracts available. Dextran based polyphenols have been synthesized and engineered to mimic the functionalities of natural tannins and these pseudotannins form nano to micro-scale colloids with PEGs of various molecular weights. In this work, the pseudotannins were complexed with PEG to make a redox responsive particle system that disintegrates upon exposure to physiological oxidative stress. These pseudotannin complexes can be used to make novel contrast agents for cardiovascular applications. They also can target phagocytic cells, and could act as both a delivery method and a direct therapeutic agent by scavenging free radicals.

Experimental Methods: Synthetic tannins were produced using a two-step process as described previously.[2] First, dextrans were substituted with benzyl protected hydroxybenzoic acids, followed by a palladium catalyzed deprotection under hydrogen gas. IPCs were formed using pseudotannins and commercially available PEGs. The antioxidant powers of IPC formulations were quantified using the Folin-Ciocalteu method[3] and disintegration of IPCs in response to superoxide was determined using a xanthine oxidase (XOD) assay. Cell uptake was performed with the phagocytic J774.2 cell line and compared to a non-phagocytic control (MDA-MB-231). Confocal microscopy (Olympus IX81) was used to visualize uptake pseudotannin particles and release of Texas Red labeled PEG in response to oxidation.

Results and Discussion: The stability of colloidal IPCs was determined by visual inspection, turbidity assays and dynamic light scattering (DLS). Stability was a function of polymer molecular weight, PEG branching, and PEG terminal groups. All colloid formulations demonstrated a range of antioxidant power, but only polygallol derived IPCs showed redox responsive decomplexation (Figure-1A-B). Phagocytic uptake of particles is indicated by punctate fluorescence in the cells (Figure-1C-D)..

Conclusion: We have demonstrated the versatility of our biomaterial platform based on naturally inspired psuedotannins. The IPC formulations decomplex when scavenging superoxide, thereby targeting and mitigating sites of inflammation. This redox sensitivity lends itself to diagnostic applications that measure oxidative levels relevant to a disease state. Additionally, IPCs can be uptaken by activated macrophages allowing delivery of therapies for inflammatory diseases. Future work will focus on developing novel contrast agents for diagnostics of cardiovascular disease.

References:

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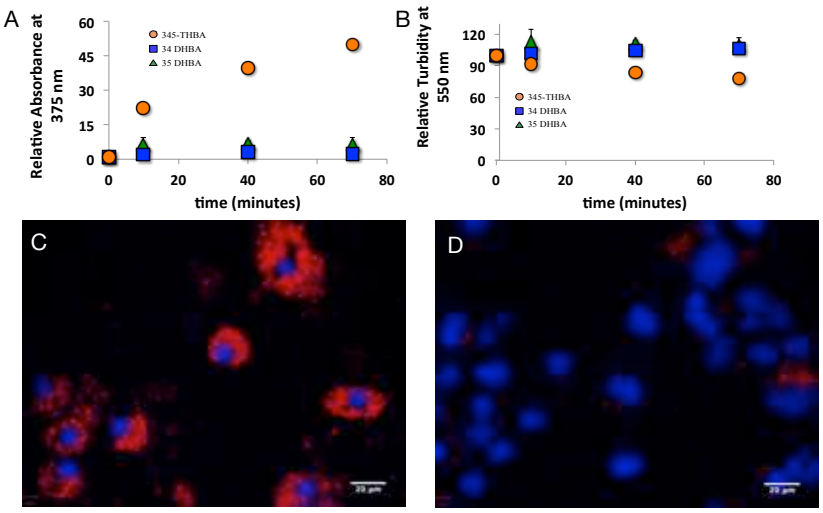

Figure-1: (A-B) XOD decomplexation assay of IPCs using 100 kDa linear PEG. Change in UV absorption (A_{375}; a) and turbidity (A_{550}; b) of IPCs in response to superoxide formation. Simultaneous changes in both properties indicate redox dependent decomplexation. (C-D) J774.2 cells (C) and MDAMB231 cells (D) were exposed to red fluorescently tagged particles. Phagocytic uptake of was confirmed with confocal microscopy. Hoechst-3342 was used as a nuclear counterstain. Scale bars represents 20µm.