Size and Chemistry Affect Cellular Distribution after Intranasal Administration of Nanoparticles

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Statement of Purpose: Size and route of administration have been shown to greatly impact the biodistribution and bioavailability of biodegradable particles.(*1-5*) For respiratory infections, intranasal administration offers many advantages, including ease of administration, induction of mucosal immunity, and reduced systemic exposure due to the localization of the delivery vehicle within the target organ.(*6*) These same properties, i.e., size and route, along with particle chemistry have been shown to influence particle uptake by antigen presenting cells (APCs), which is an essential first step in the induction of an adaptive immune response for vaccines or as the first line of defense against exogenous particles.(*7-9*)
For particle size comparative studies, many researchers utilize non-degradable particles. In this work, the synthesis of monodisperse biodegradable polyanhydride particles of multiple sizes has enabled the quantitative evaluation of the role of particle size and chemistry upon cellular distribution after intranasal administration.

Methods A murine model was utilized to evaluate the biodistribution of intranasally administered monodisperse poly(sebacic anhydride) (poly(SA)) and commercial polystyrene (PS) particles with nominal sizes of 250 nm, 470 nm, and 2.5 µm. Particles were administered as a suspension intranasally to anesthetized mice. Biodistribution was evaluated using fluorescent imaging of excised organs at 6 h, 12 h, 24 h, and 24 h post administration. Cellular uptake and differentiation was evaluated for the excised lungs by labeling whole tissue homogenates for cell surface markers representing specific cell types (CD11b, CD11c, F4/80, and Ly6C/G).

Results: The deposition of intranasally administered particles in suspension was dependent on primary particle size, with maximal deposition occurring with the 470 nm poly(SA) and the corresponding PS particles. However, particle interactions with respiratory cells were found to be dependent on size, chemistry and time. The percentage of lung tissue homogenate positive for particles was consistent between chemistries at the 250 nm and 470 nm sizes. In contrast, there were significant differences between chemistries with the 2.5 µm particles.

The particle positive cell populations were further characterized into different cell types based on cell surface marker expression (Fig. 1). Statistically significant differences in the phenotypes of the cells associated with particles were observed based on particle size, chemistry, and time post administration.

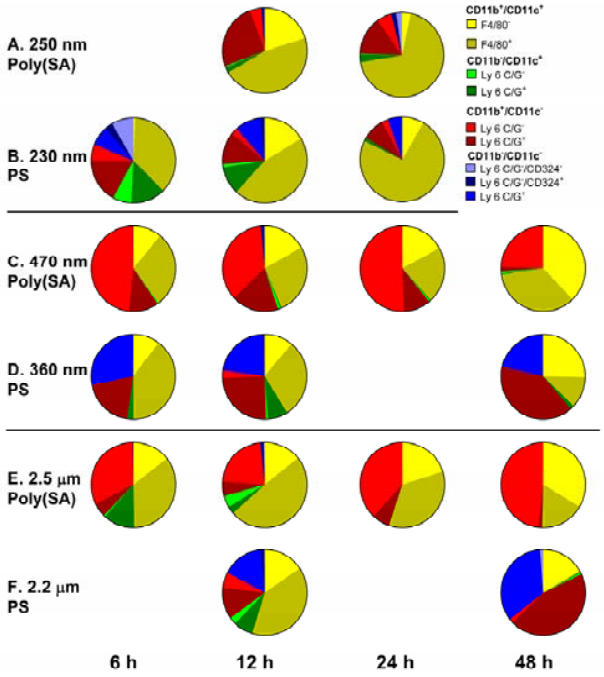

Fig. 1. Phenotypes of particle-positive cells from the lung tissue homogenate. Each pie chart shows the average cellular phenotype from the particle-positive cell population for that particular chemistry and size of particle for each time point post administration. The area, by color, shows the respective quadrant of CD11b/CD11c gated cells with different subpopulations delineated by shading (n = 10).

Conclusions: The synthesis of monodisperse polyanhydride particles of multiple sizes has enabled the investigation into the roles of particle size, chemistry, and the dynamics of degradation on the deposition and biodistribution of particles. In this work, particle size, chemistry, and kinetics were identified to be important factors affecting the specific type of particle-cell interaction, and cellular trafficking of the particles out of the lung.

References:

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