Nanoparticles and the lung: friend or foe?

Y. S. Prakash\textsuperscript{1,2} and Sadis Matalon\textsuperscript{3}

\textsuperscript{1}Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota; \textsuperscript{2}Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota; and \textsuperscript{3}Department of Anesthesiology, University of Alabama Birmingham, Birmingham, Alabama

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Prakash YS, Matalon S. Nanoparticles and the lung: friend or foe? Am J Physiol Lung Cell Mol Physiol 306: L393–L396, 2014. First published January 24, 2014; doi:10.1152/ajplung.00013.2014.—Nanomedicine is a rapidly evolving field with high potential for developing novel research, diagnosis, and/or therapeutic approaches for lung diseases. However, for engineered nanomaterials to reach their true potential, there are still a number of unanswered questions regarding nanomaterial vs. tissue properties that dictate lung cellular uptake, distribution, and intracellular effects, and particle vs. tissue factors that determine toxicity vs. beneficial effects in the lung. Some of these key questions are highlighted in this Perspectives. Addressing these important issues will help improve nanoparticle design and enhance enthusiasm for more widespread use of nanotechnology in pulmonary medicine.

Address for reprint requests and other correspondence: Y. S. Prakash, Dept. of Anesthesiology, Mayo Clinic, Rochester, MN 55905 (e-mail: prakash.ys@mayo.edu).
currently hindered by a substantial knowledge gap in our understanding of what factors determine the relative beneficial effects of nanoparticles in lung tissues (be it normal or pathological) vs. the toxicity of such nanoparticles, particularly as unintended consequences in normal tissues. This key question envelops many more fundamental issues:

1) Which nanoparticle properties are most important in determining their distribution, uptake, and half-life within different lung compartments: core vs. overall particle size, nature of ligands, surface charge, hydrophobicity, tendency toward aggregation, etc. (5, 21, 22, 26, 51)?

2) How do nanoparticle interactions with biological fluids (mucus, blood) or cell surfaces affect the nanoparticle surface itself (concepts such as the protein “corona”) and its further ability to interact with tissues (11, 16, 34, 38, 58, 59)?

3) What lung cellular properties are important in nanoparticle-cell interactions, uptake, and intracellular processing and targeting (20, 31, 36, 37, 63)? Here, an important corollary issue is what nanoparticle vs. cellular properties determine intracellular fate vs. unobstructed translocation of nanoparticles across the bronchial vs. alveolar epithelium. This is particularly relevant for design of nanoparticle-based drug delivery systems for proximal airways (where the epithelium as well as underlying structures such as smooth muscle, fibroblasts, and immune cells may need to be targeted) vs. the distal lung parenchyma.

Fig. 1. Issues in identifying nanoparticles (NP) as friends vs. foes. Inhalation of nanoparticles, be it intentional or not, can result in widespread distribution within the lung, where their eventual effects on different lung compartments are driven by a host of nanoparticle- vs. host-dependent factors. In terms of the nanoparticle itself, factors such as core material, core vs. overall size (following conjugation of ligands with surface engineering), tendencies to collect proteins within biological media (corona) and toward aggregation may all play an important role in the uptake, distribution, cellular effects, and elimination of nanoparticles. At the level of the proximal airway, nanoparticles will need to penetrate the mucus and epithelial ciliary layer to produce effects. This requirement may drive nanoparticle design if the intent is to target bronchial epithelium and underlying structures with the goal of therapies for inflammatory or fibrotic airway diseases. At the alveolar level, penetration of nanoparticles may lead to effects in the pulmonary vasculature as well. Within different areas of the lung, nanoparticles may modulate the immune response. In all of these processes, cellular uptake, translocation, and transfer of nanoparticles may be driven by mechanisms such as clathrin-coated vesicles, caveolae, and pinocytosis. Intracellular effects of nanoparticles may be cell and context specific, overall resulting in a balance between detrimental and potentially beneficial effects in the lung. ROS, reactive oxygen species; ASM, airway smooth muscle.
4) What are the key cellular mechanisms that underlie nanoparticle effects in lung cells (reactive oxygen species, physical interactions, inflammasome pathways, mitochondria) (6, 25, 29, 41)?

5) What are the detrimental/pathological effects of nanoparticles in the lung (e.g., inflammation, fibrosis, cancer) (29, 33, 49, 50)?

6) Do normal lung cells and tissues differ from pathological tissues in nanoparticle interactions (e.g., in the presence of thicker mucus as occurs in cystic fibrosis or bronchiitis, in the presence of blood, or remodeled, thicker epithelium as in asthma)? These issues may help us design nanoparticles to be largely beneficial with negligible toxicity, whether as drug delivery systems or as self-therapeutic moieties.

7) How should we design nanoparticles in a “target-specific” manner? Presumably if the goal is to target diseases such as asthma in which it is normal airway and immune cells gone awry, this will require nanoparticle therapies that do not disrupt normal epithelial barrier function or worsen immune responses in the airway. On the other hand, if the target is focal cancers, the goal would be intentional but targeted cellular toxicity, with minimal effects on surrounding normal tissues.

8) What are the systemic/nonpulmonary effects of nanoparticles with local or systemic administration (inflammation, thrombosis, neurogenic effects)? A particularly important concern may be whether nanoparticles can cross placental barriers and influence development of the fetus.

9) What are the best techniques for measuring nanoparticle concentrations and distribution in lung compartments (28)?

In addition to the above concepts of nanoparticles in diagnostic and therapeutic medicine, there is increasing interest in the idea of their use in in vitro screening and identification of biomarkers (1, 32). Here, our understanding of how nanoparticle interactions with biological materials (blood, serum, sputum, cell surfaces, lysates) affect nanoparticle themselves (e.g., formation of a protein corona) could be used advantageously to develop novel testing platforms. Conversely, development of tests and biomarkers for nanoparticle effects in the lung will also be necessary. Here, in vitro lung cell test platforms (e.g., alveolar cell, fibroblast, or endothelial monolayers) and identification of relevant serum or sputum biomarkers will be of particular interest. These novel approaches will also be instrumental in identifying the mechanisms by which nanoparticles influence lung cells.

The above discussion, although necessarily brief and certainly not comprehensive, nonetheless emphasizes the overall urgent need for much deeper and greater understanding of nanoparticles in the lung in order for nanomedicine to become a reality. This will require interdisciplinary and collaborative research between material scientists/nanoparticle engineers, lung cell and molecular biologists and physiologists, and immunologists. Studies are clearly needed to identify and highlight key concepts of nanoparticle design, implementation, and utilization in targeting lung diseases (the friend) with minimal pulmonary or vascular toxicity (the foe) and the current and future challenges in making this a reality (Fig. 1).

REFERENCES


