Shifting Paradigms in Pulmonary Drug Delivery: From Aerosols to Biological Barriers

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ABSTRACT SUMMARY

The pulmonary route has tremendous potential both for local and systemic delivery of macromolecular biopharmaceuticals as well as of small organic molecules. However, as the famous case of insulin shows, improving aerosol technology alone is obviously not sufficient. Relevant biological barriers of the respiratory tract encountered after aerosol deposition comprise both cellular (e.g. AT-1/II cells, macrophages) as well as non-cellular elements (e.g. mucus and surfactant).

This presentation reports on recent approaches of our lab to develop innovative in-vitro models and drug carriers, which we feel, are necessary for understanding and developing advanced pulmonary drug delivery systems.

INTRODUCTION

Until recently, pulmonary drug delivery was essentially a matter of aerosol science and technology, striving to optimize particles and/or devices for efficient pulmonary deposition after inhalation. Maximizing deposition in the deep lung and minimizing deposition in the throat used to be the generally accepted paradigm for an optimal aerosol formulation. But is this actually sufficient?

Of course it is not! Oral drug delivery, where reaching the site of absorption (=GI tract) is relatively trivial, shows that this is only a necessary, but not sufficient condition for efficient drug delivery. Grace to remarkable progress in aerosol technology, efficient and reproducible deposition in the deep lung is meanwhile a reality. Therefore, however, it is high time to address the following questions concern the fate of aerosol particles after deposition:

1. Is the deposited API sufficiently permeable to cross the alveolar epithelium, regardless of its large surface area?
2. Are solubility and dissolution rate in the pulmonary lining fluids sufficient, especially considering its small volume?
3. How to control clearance processes (e.g. by mucus or macrophages) of potential pulmonary controlled-release formulations?

In order to address these emerging issues, both novel in-vitro test systems - preferentially based on mammalian sources - as well as novel carrier systems – often based on nanotechnology – are urgently needed.

EXPERIMENTAL METHODS

Human alveolar epithelial cells were isolated from biopsy material after lung surgery, patient consent and ethical approval being on file (1). After transfection by lentiviral vectors in combination with a set of more than 33 immortalizing genes, they were characterized regarding cell-specific markers and barrier properties (2)

For dissolution testing aerosol particles were collected on regenerated cellulose membranes using an abbreviated Andersen cascade impactor and transferred to different set up’s (e.g. modified paddle apparatus, flow through cell or Franz diffusion cell) (3)

Aerosolizable microfibers were generated by template-assisted polyelectrolyte encapsulation of nanoparticles (4)

The adsorption of proteins to nanoparticles in the context of macrophage uptake was studied by atomic force microscopy (AFM) and analytical ultracentrifugation (5,6).

The relationship between microstructure of pulmonary mucus and nanoparticle penetration was studied by cryoelectronmicroscopy and optical tweezers (7).
RESULTS AND DISCUSSION

Human alveolar epithelial type 2 cells can be grown as monolayers on permeable filter supports, developing typical type 1-like characteristics and tight intercellular junctions with high transepithelial resistance (>1000 Ω cm²) and low paracellular permeability (1). These essential features could also be maintained after immortalization in several cell lines, creating the perspective to develop some standardized in-vitro model for alveolar deposition and permeability studies (2).

For studying the release of active compounds from aerosol particles in dissolution media relevant to pulmonary delivery, it was surprisingly found that the USP paddle apparatus after modification with some membrane holder has the best discrimination power and reproducibility (3).

Template-assisted encapsulation of nanoparticles by alternating infiltration of polycations and polyanions allowed producing colloidally dispersable, nanostructured microfibers (4). The same technique could also be adopted to produce microfibers of biocompatible materials, such as mannitol, lactose or agarose, containing beta-mimetic drugs and allowing to study their uptake by macrophages (see figure).

The surfactant-associated proteins A (SP-A) and D (SP-D) showed different adsorption to magnetite nanoparticles (mNP) with either more hydrophilic (starch) or hydrophobic (phosphatidylcholine) surface modification, leading in both cases to an increased uptake by alveolar macrophages. However, synthetic surfactant lipid and isolated native surfactant preparations significantly modulated the effects exerted by SP-A and SP-D, respectively, resulting again in comparable levels of macrophage interaction for both hydrophilic and hydrophobic nanoparticles (6). These data point to the importance of such protein/lipid-corona for the subsequent disposition of particles when deposited in the lung.

By comparing the interaction of mNPs with equi-viscous preparations of native respiratory mucus and synthetic model hydrogels, we found remarkable differences between microscopic diffusion behaviour and macroscopic penetration. CryoEM images and active probing by optical tweezers revealed a broad pore size distribution but particularly high rigidity of the mucin scaffold as reasons for the observed particle immobilization (7).

CONCLUSION

Innovative in-vitro models and carrier systems are instrumental to successfully cope with the biological barriers of the respiratory tract after deposition of aerosol medicines in the future.

REFERENCES


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