Epithelix

in vitro Solutions for Respiratory Diseases and Chemical Testing

Goblet cell metaplasia induced in a fully differentiated human airway epithelium (MucilAir ™)

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Up to now, goblet cell metaplasia is induced during the differentiation phase of the human airway epithelium by TH-2 cytokines like IL-13 and IL-4 (Atherton et al., 2003; Tanabe et al., 2007; Booth et al., 2007). Such *in vitro* models may not reflect what happens in vivo in patients suffering respiratory diseases such as such as asthma, COPD, and Cystic fibrosis. Indeed, the differentiation of the ciliated cells was totally inhibited by 10 ng/ml of IL-13. In this work, we would like to induce Goblet cell metaplasia in a fully differentiated human airway epithelium, MucilAir™.

The epithelia were treated during two weeks with IL-13 at different concentrations, ranging from 0.3 to 30 ng/ml. Using *in situ* Alcian Blue staining, as well as histological analysis, we demonstrated that MucilAir™ showed an increased goblet cell density after 14 days of IL-13 treatment, in a dose-response manner. Furthermore, ELISA analysis revealed a concomitant increase of Eotaxin-3 released in the culture media in function of IL-13 concentration. Interestingly, the ciliated cells were still present, and the muco-ciliary clearance is still functional, despite of an over-production of mucus.

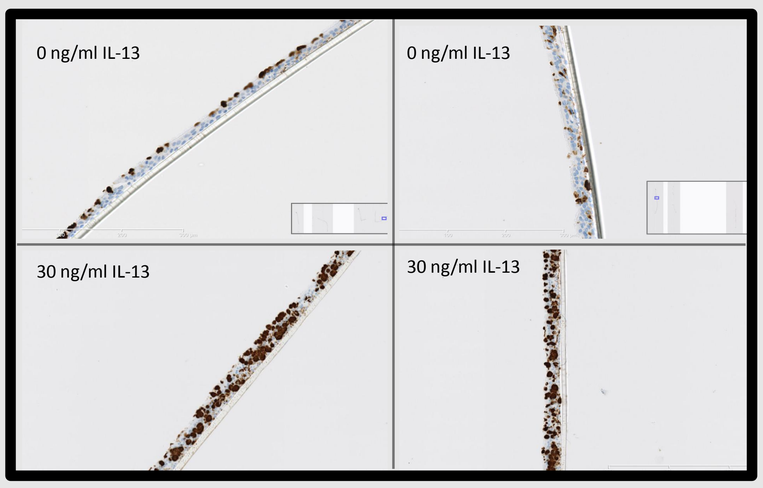
This process was reversible: the morphology and the number of the goblet cells are similar to the non-treated epithelium two weeks later after the withdraw of IL-13 from the culture medium, this results is consistent with the recent clinic trials demonstrated that blocking IL-13 signaling improved the lung function of the asthmatic patients.

The end results from several different batches of MucilAir are very similar, therefore reproducible. Taken together, it is possible to induce Goblet cell metaplasia in a fully differentiated human airway epithelium model. We believe that this model is closer to what happens in vivo, therefore, a better and more reliable *in vitro* cell model for studying, and for assessing the efficacy of the drug candidates for treating asthma, COPD and Cystic Fibrosis.

The advantages of MucilAir™

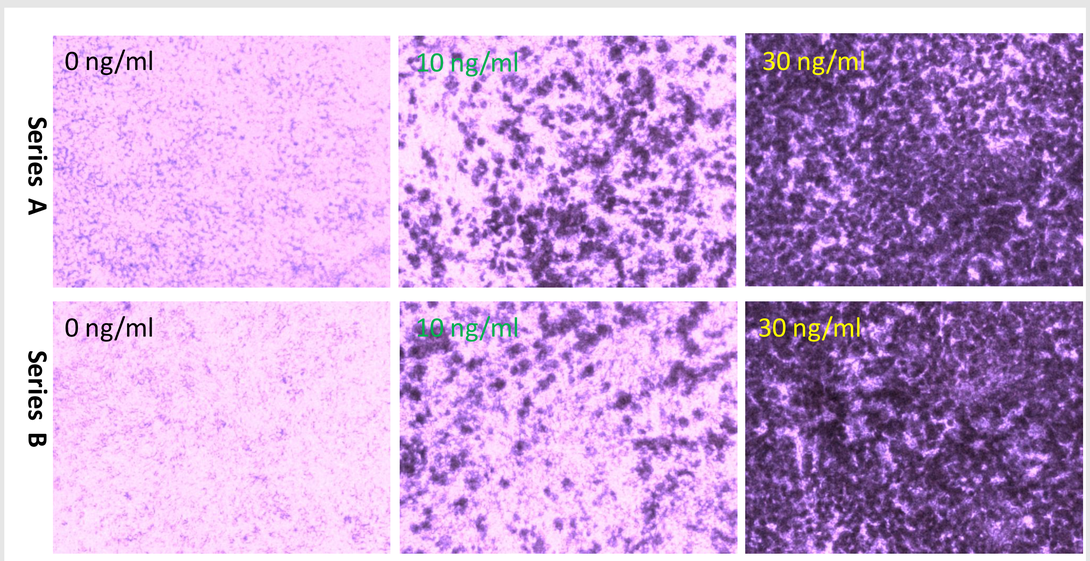
- It is composed of **primary human respiratory cells.**
- It **mimics** the morphology and functions of the native human airway epithelium.
- It has a **unique shelf-life of 12 months**.
- Epithelia from **different pathologies** are available (asthma, COPD, CF, allergic rhinitis).
- It is **ready and easy to use**.

Histological Analysis of IL-13 treated Cells



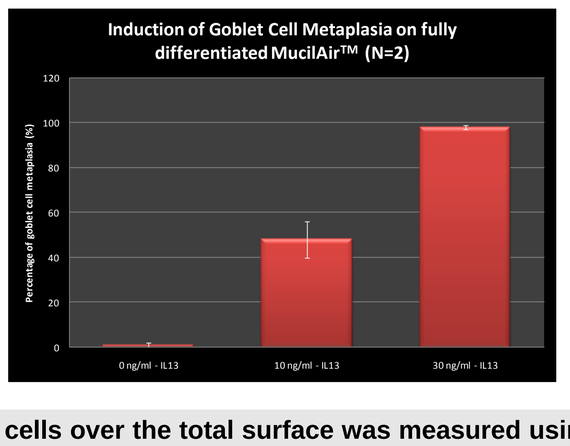
The figures depict Paraffin sections stained with anti-Muc-5Ac antibody from 2 batches of MucilAir™

Dose-dependent increase of the goblet cell density In fully differentiated MucilAir upon IL-13 treatment



Fully differentiated MucilAir (>45 days of culture, from one donor) were treated with 10 ng/ml or 30 ng/ml of IL-13 during 14 days. The culture media were changed every 2 days. At D14, the epithelia were fixed in 4% Formaldehyde and stained *in situ* with Alcian Blue (Goblet cells stained blue). The pictures were taken on a contrast microscope (Zeiss Axiort 250) with a 10X objective.

Quantifications of goblet cells



Percentage of the blue cells over the total surface was measured using Software ImageJ, showing a dose-dependent increase of the goblet cell density induced by IL-13 at Day 14.

Conclusion

Taken together, MucilAir™ is a good, reliable *in vitro* cell model for studying goblet cell metaplasia, and for assessing the efficacy of novel drug candidates for treating respiratory diseases like asthma and COPD.

Acknowledgements

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Ligue suisse contre la vivisection

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