Characterisation of MRP1 in human distal lung epithelial cells *in vitro*

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Drug Delivery to the Lungs 27
Edinburgh, Scotland

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Multidrug resistance-associated protein 1 transport cycle
Clinically relevant substrates of ABC transporters

- ABCG2
  - Lysotracker
  - Pheophorbide α
  - Riboflavin
  - Doxorubicin
  - Mitoxantrone
  - Etoposide
  - Methotrexate
  - Folic acid
  - Estrone-3-sulfate
  - Cyclophosphamide
  - Hydroxyurea
  - Cisplatin

- Pgp
  - Hoescht 3342
  - Topotecan
  - Rifampicin
  - Paclitaxel
  - Colchicine
  - Mitomycin

- MRP1
  - Glutathione (GSH, GSSG)
  - Glutathione conjugates
  - Glucuronide conjugates
  - Sulphate conjugates

Stacy et al. (2013) Mpl Pharmacol
ABC transporter expression analysis in lung tissue and cells


Endter et al. (2009) J Pharm Pharmacol
MRP1 abundance is linked to COPD

van der Deen et al. (2006) Virchows Arch
Aims of the study

Determine the cellular localisation and activity of MRP1 in freshly isolated human AT2 and AT1-like cells in primary culture

Investigate whether expression and activity in the NCI-H441 cells line is comparable to that in primary cells

Study the influence of culture conditions on MRP1 expression

Measure the effect inhaled pharmaceuticals have on MRP1 activity *in vitro*
MRP1 expression in human alveolar epithelial cells

Data represent means ± SD, n = 3.
MRP1 expression in the NCI-H441 cell line

Data represent means ± SD, n = 6.

Culture conditions

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<th>Passage number</th>
<th>AIC</th>
<th>LCC</th>
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MRP1

β-actin
MRP1 is localised to the basolateral cell membrane

Surface protein biotinylation, Ap and Bs, indicate apically and basolaterally sulfo-NHS-biotin treated cells, respectively, and C indicates whole cell lysate.

Bi-directional CF(DA) efflux, data represent means ± SD, n = 6. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001
MRP1 causes net absorption of carboxyfluorescein (CF)

Data represents means ± SD, n = 4, *p ≤ 0.05, **p ≤ 0.01.
CSE up-regulates MRP1 expression in NCI-H441 cells

Data represent means ± SD, n = 3, *P < 0.05
Inhaled drugs interact with MRP1
Summary and Conclusions

MRP1 is functionally expressed to the basolateral membrane of human distal lung epithelial cells \textit{in vitro}.

MRP1 expression and activity are comparable in primary cells and the NCI-H441 cell line.

LCC vs. AIC culture conditions do not seem to have significant effects on MRP1 expression.

Tobacco smoke extract up-regulates MRP1 levels.

Inhaled pharmaceuticals have an effect on MRP1 activity \textit{in vitro}.

MRP1 might therefore be of importance as a drug target in COPD (and other lung diseases).
Acknowledgements

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