Targeting extracellular protein disulphide isomerase to control Burkholderia cenocepacia lung infections

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Background. We have shown that the interaction between Burkholderia cenocepacia and lung epithelial cells is mediated by redox sensitive enzymes of the protein disulphide isomerase (PDI) family, in particular by ERp57. In fact, either thiol reactive agents (DTT, GSH, and DTNB) or ERp57 inhibitors are able to drastically reduce the adhesion and the invasion of B. cenocepacia into epithelial cells and to attenuate the pro-inflammatory response elicited by bacteria. These observations suggest that defects in GSH export in the airway surface liquid, observed in cystic fibrosis (CF) patients, may favour B. cenocepacia infection.

Hypothesis and objectives. ERp57 inhibitors, in particular epigallocatechin-3-gallate (EGCG), the most abundant green tea catechin, could be useful in therapies aimed at controlling Burkholderia lung infection in CF patients. To this aim we have evaluated: 1) the effect of EGCG on Burkholderia infection in different cell types; 2) the effect of EGCG on Burkholderia intracellular replication; 3) the efficacy of EGCG in infected mice.

Methods. The effects of EGCG on B. cenocepacia infections have been investigated either in epithelial or macrophage cell lines and preliminary tests have been carried out to evaluate its efficacy in mice.

Results. We have obtained convincing evidence that ERp57 plays a role in Burkholderia infections in respiratory epithelial cells. In fact, we have demonstrated that EGCG is able to strongly reduce IL-8 and IL-6 release and IL-8, IL-1β and TNFα expression levels in epithelial cells infected by Burkholderia. In contrast, we have not observed any involvement of PDI in the uptake and intracellular survival of B. cenocepacia into differentiated monocytes. Within these cells, Burkholderia survives and replicates by evading autophagy through the inhibition of the autophagolysosome formation and the alteration of the phosphorylation state of mTOR and S6Kinase. The pre-stimulation of autophagy into macrophages limits Burkholderia intracellular survival. In order to test the possible ability of EGCG to limit Burkholderia lung infections we have carried out pilot experiments to optimize bacterial infective dose and drug administration in endotracheally infected mice.

Spin-off for research & clinical purposes. This study has provided preliminary evidences supporting the usefulness of EGCG in therapies aimed at the control of B. cenocepacia in CF lung. In perspective, it could be interesting hypothesize a combined therapy based on EGCG and autophagy inducers.

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