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### **Association of host cell glutathione metabolism with *Chlamydia pneumoniae* infection phenotype**

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**BACKGROUND:** The widely spread intracellular pathogen *Chlamydia pneumoniae* has been related to several chronic inflammatory conditions, in addition to respiratory tract diseases. A key factor in that association is the ability of *C. pneumoniae* to persist in host tissues and thus maintain the chronic inflammation. Macrophages play a central role in this phenomenon as *C. pneumoniae* infection in them turns to persistent mode without exogenous triggers. The availability of nutrients, e.g. amino acids, is an important factor in chlamydial persistence. As the primary cellular cysteine source, glutathione (GSH) can thus be expected to affect *C. pneumoniae* infection outcome. We have previously reported that GSH levels are elevated in *C. pneumoniae* infection in THP-1 macrophages and GSH supplementation increases *C. pneumoniae* infectious progeny production in these cells, indicating a shift towards more productive phenotype<sup>1</sup>.

**OBJECTIVES:** To study the association of cellular GSH metabolism with *C. pneumoniae* infection during both persistent and productive infections.

**METHODS:** The impact of GSH depletion with diethyl maleate (DEM) and buthionine sulfoximine (BSO) on *C. pneumoniae* infectious progeny production was studied in THP-1 macrophages and A549 epithelial cells. RT-PCR on genes involved with GSH metabolism was performed in infected THP-1 cells.

**RESULTS:** When infected THP1- macrophages were treated with 200 µM DEM, which sequesters cellular GSH by forming a chemical adduct, infectious progeny production decreased dramatically. Also the GSH synthesis inhibitor BSO (250 µM) decreased the infectious progeny production, but less effectively, yet BSO was superior to DEM in depleting GSH levels. Similar results were obtained with A549 cells harbouring a productive *C. pneumoniae* infection: DEM was more effective in suppressing infectious progeny production while BSO had a more drastic effect on cellular GSH pools. Based on these observations, it can be speculated that while GSH itself affects the infection outcome by maintaining a favourable redox milieu, the constituents of this tripeptide drive the productive *C. pneumoniae* infection. This hypothesis is also supported by our gene expression analysis revealing that intracellular GSH degrading enzyme, ChaC1, was upregulated during the infection. In addition, A549 cell GSH levels were found to decrease during the productive infection. Collectively, this work suggests that availability of GSH-derived amino acids are key factors influencing the *C. pneumoniae* infection phenotype.

<sup>1</sup> Taavitsainen, E., Kortesoja, M., Bruun, T., Johansson, N. G., & Hanski, L. *Molecules*, 2020.