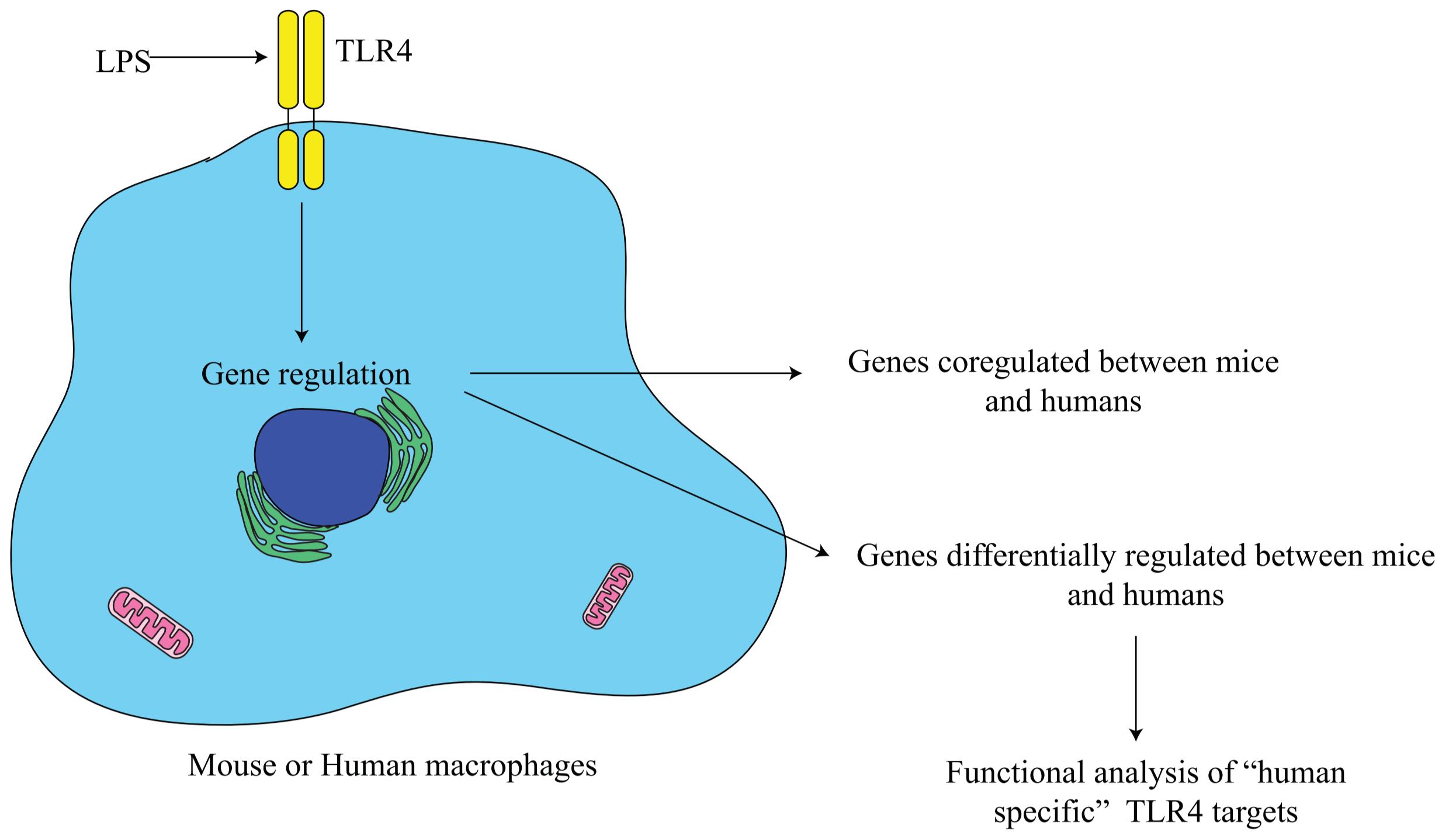
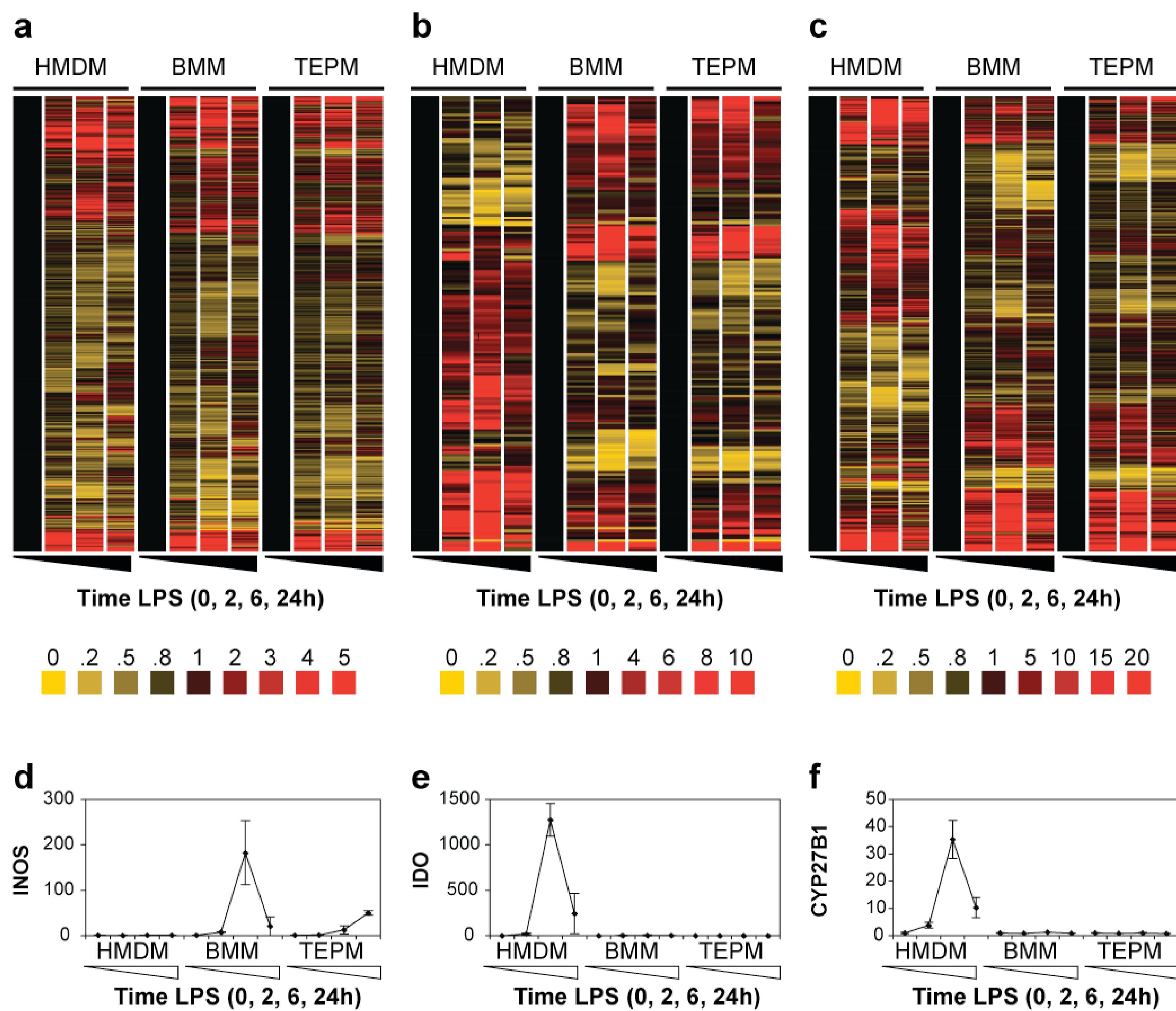


I Introduction

- Mice are widely used as models to study infection and immunity, but there are many differences in the immune responses of mice and humans [1,2]
- These differences can partly be attributed to the coevolution of the host immune system as a response to rapidly evolving pathogens
- The innate immune system recognizes invading microbes through pattern recognition receptors such as Toll-like Receptors (TLRs) [3]
- This study used cross-species expression profiling to identify co-regulation and divergence in LPS (TLR4) responses between primary human and mouse macrophages, and investigated the functions of “human-specific” pathways in the anti-microbial response to *Salmonella enterica* serovar typhimurium (SL1344)



II Expression profiling of human and mouse macrophage responses to LPS

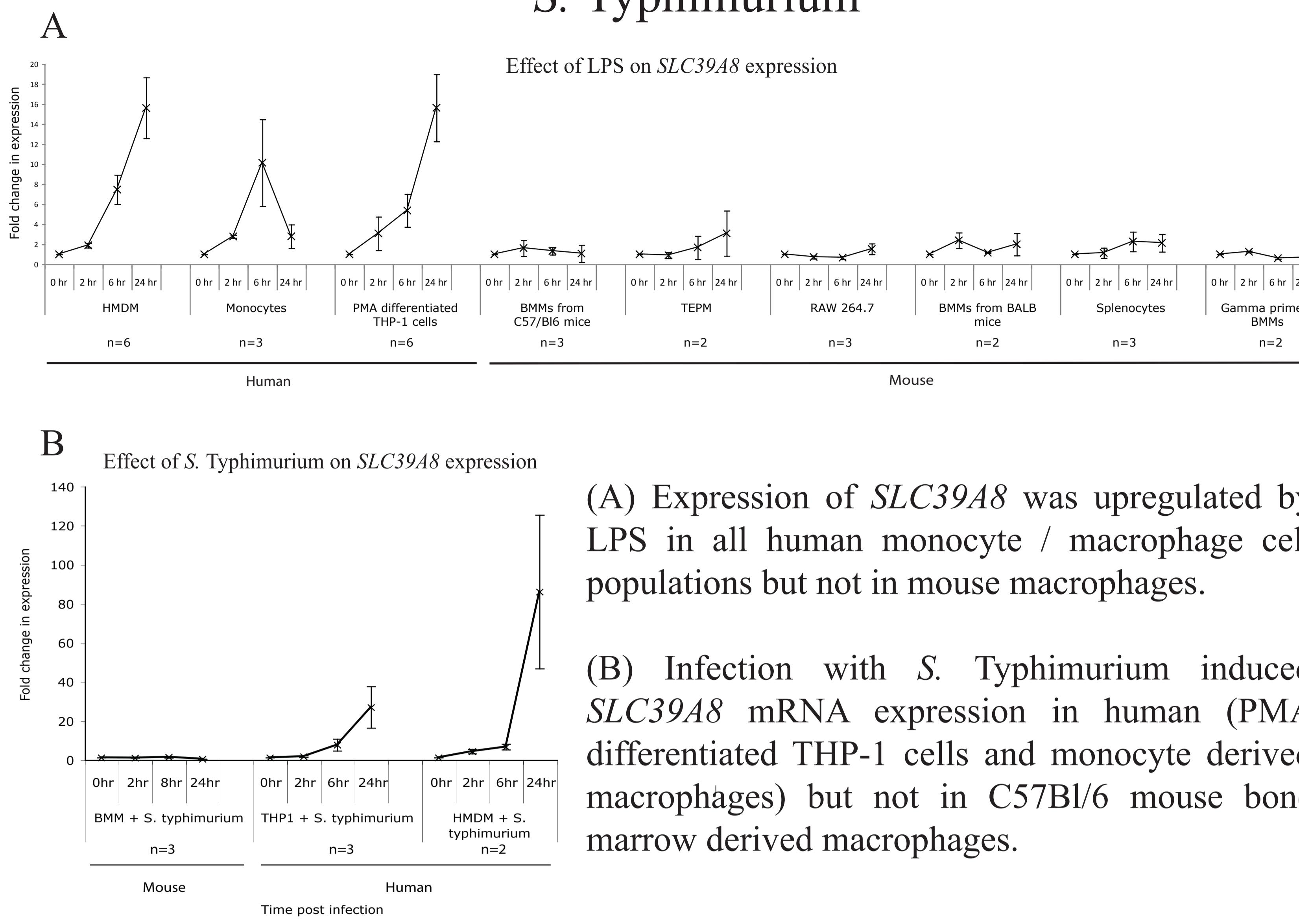


- Expression profiling of human (HMDM) and mouse (BMM and TEPM) macrophages over an LPS time course revealed that (a) 80% of the genes were co-regulated between the two species while (b and c) 20% of the genes were divergently regulated.
- Many anti-microbial effector genes were differentially regulated, e.g. *iNOS*, *IDO*, *CYP27B1* (d, e and f)
- Several ion channel genes were specifically upregulated in human macrophages; one of these was the zinc ion importer *SLC39A8* [4]
- The role of zinc as an essential micronutrient involved in maintaining a healthy immune response has been well documented [5,6]
- A recent clinical trial showed that Zn decreased morbidity of gastrointestinal tract infections in children and infants [7]

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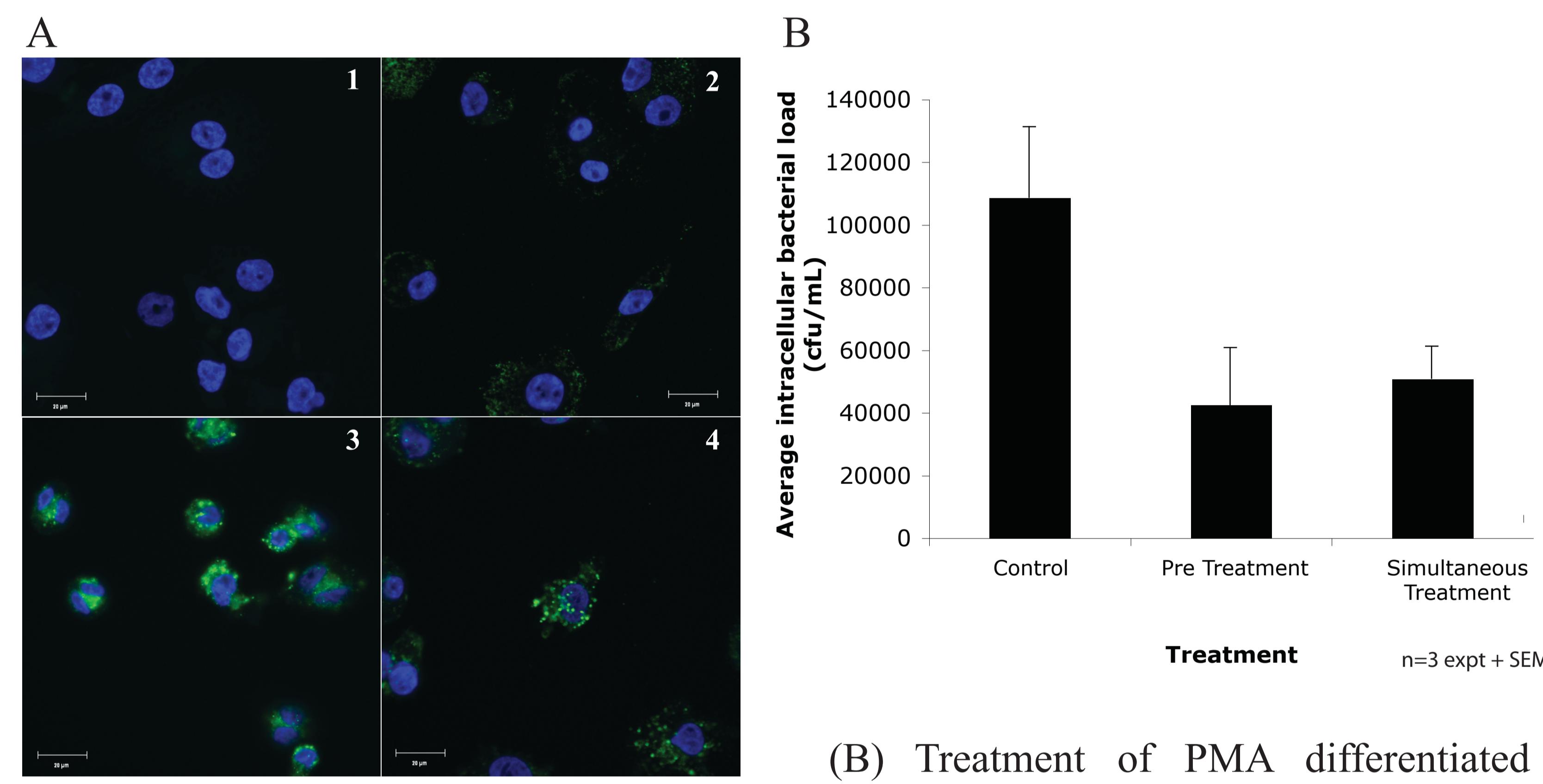
III Expression of *SLC39A8* mRNA was upregulated in human but not mouse macrophages by LPS or infection with *S. Typhimurium*



(A) Expression of *SLC39A8* was upregulated by LPS in all human monocyte / macrophage cell populations but not in mouse macrophages.

(B) Infection with *S. Typhimurium* induced *SLC39A8* mRNA expression in human (PMA differentiated THP-1 cells and monocyte derived macrophages) but not in C57Bl/6 mouse bone marrow derived macrophages.

IV Zinc decreases intracellular survival of *S. typhimurium* in PMA differentiated THP-1s and is localized within vesicles as a response to LPS



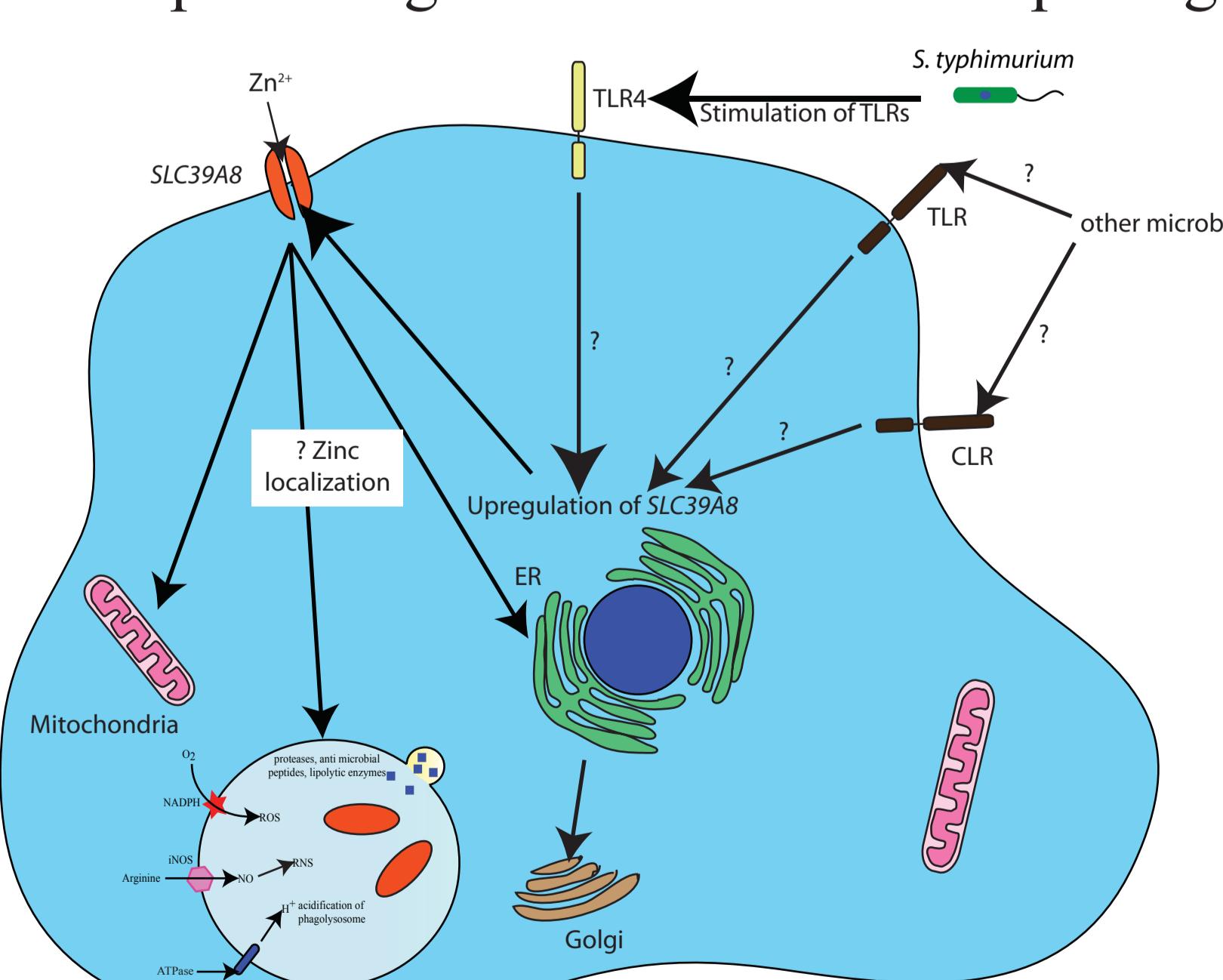
(A) Zn is localized within PMA differentiated THP-1 cells in discrete vesicles as a response to LPS (1) PMA differentiated THP-1 cells only, (2) PMA differentiated THP-1 cells treated with FluoZin-3, (3 and 4) PMA differentiated THP-1 cells treated with LPS and FluoZin-3.

(B) Treatment of PMA differentiated THP-1 cells with Zn either 1hr prior to infection or at the time of infection resulted in a decreased intracellular bacterial load at 24hrs post infection

V Conclusion

SLC39A8 was induced in human, but not mouse macrophages in response to pathogen challenge, and may play a role in antimicrobial responses against the intracellular pathogen *S. typhimurium*.

We hypothesise that the stimulation of TLRs by *S. typhimurium* results in the upregulation of expression of *SLC39A8*. This results in increased uptake of Zn by the macrophages. This Zn is then utilised by the cells in antimicrobial responses such as the production of ROS and/or is incorporated into enzymes involved in antimicrobial mechanisms.



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