Involvement of ion channels in human macrophage antimicrobial responses

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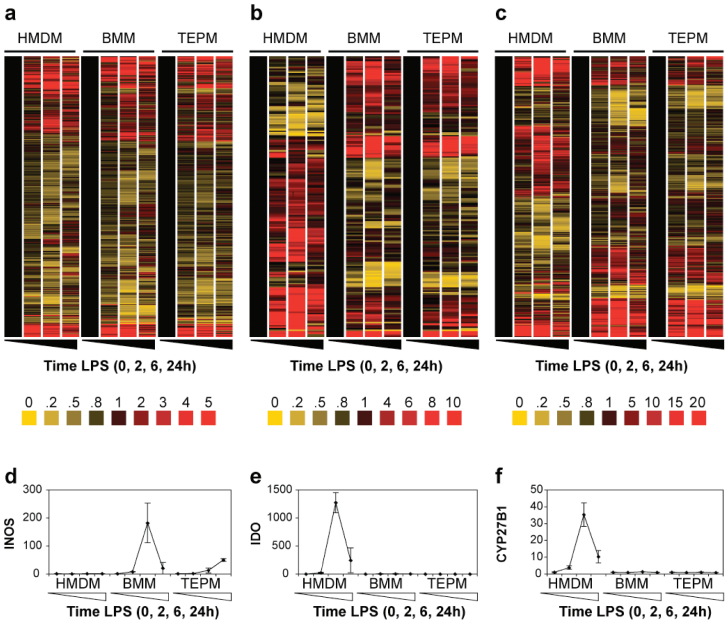
Introduction

- Mice are widely used as models to study the structure and function of the immune sytem, but there are many differences in the immune responses of mice versus humans [1,2]
- These differences can partly be attributed to the co-evolution 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)

Expression profiling of human and mouse macrophage responses to LPS

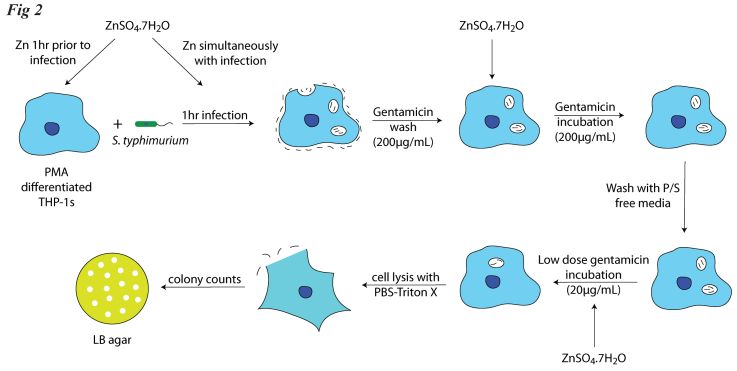
Fig 1



- Expression profiling of human (HMDM) and mouse (BMM and TEPM) macrophages over an LPS timecourse 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*
- 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 doccumented [5,6]
- A recent clinical trial showed that Zn decreased morbidity of gastrointestinal tract infections in children and infants [7]

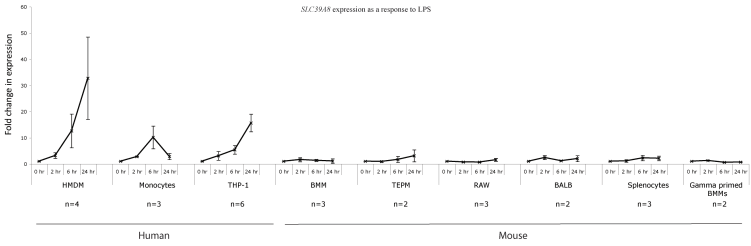
Infection assay to assess the intracellular survival of *S.* typhimurium in PMA differentiated THP-1 cells

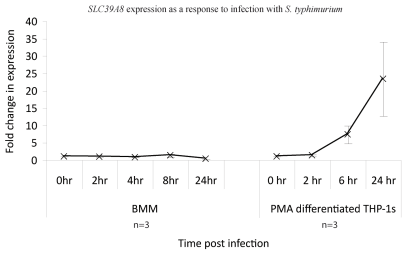
Fig 2



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

Fig 3

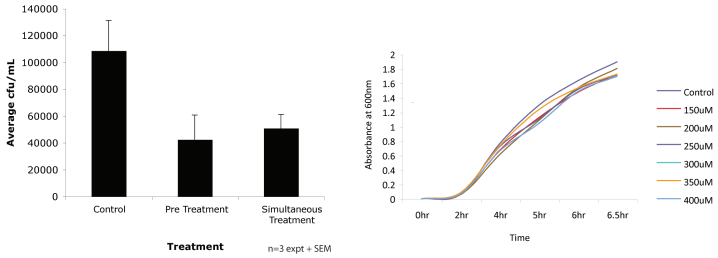




- Expression of *SLC39A8* was upregulated by LPS in all human monocyte / macrophage cell populations but not in mouse macrophages
- *SLC39A8* was upregulated in PMA differentiated THP-1s (a human macrophage like cell line) but not in C57Bl/6 mouse bone marrow derived macrophages by infection with *S.* typhimurium

Zinc decreases intracellular survival of *S.* typhimurium in PMA differentiated THP-1s

Fig 4



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

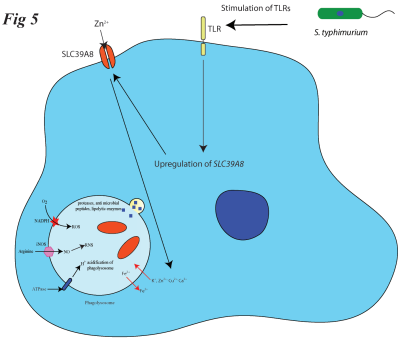
Zn had no effect on *Salmonella* growth in LB broth

Conclusion

SLC39A8 is induced in human, but not mouse, macrophages in response to pathogen challenge, and may play a role 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

Fig 5



References

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