TECHNICAL BULLETIN

Zinc Supports Mitochondrial Health and Macrophage Function During Bacterial Challenge

Introduction

Macrophages are first-line immune cells that require healthy mitochondria to support bacterial clearance. Zinc (Zn) plays important roles in immune regulation, mitochondrial function, and cellular energy metabolism. This technical bulletin summarizes the effects of Zn status and Zn supplementation on mitochondrial biogenesis, mitochondrial health, and antibacterial activity in macrophages challenged with *Mycobacterium avium* complex (MAC). It is known that MAC is the most common cause of non-tuberculous mycobacterial disease (NTM), accounting for 70 to 80% of all NTM infections worldwide. Prevalence rises sharply after age 65. Women over 60 account for the majority of pulmonary MAC cases.

Study Objective

To evaluate the effects of Zn deficiency and Zn supplementation on mitochondrial function and antibacterial activity in macrophages during a bacterial challenge.

Experimental Models & Key Terms

- U937 human macrophages: routine *in vitro* research model for human monocytes and macrophages
- ZIP8 KO BMDM: bone-marrow derived macrophages (BMDMs) extracted from mice with a knockout (KO) of the ZIP8 gene; ZIP8 encodes a crucial metal ion transporter responsible for cellular Zn and Mn
- PGC-1α & TFAM: key regulators of mitochondrial biogenesis and function
- Mitochondrial biogenesis: the cellular process of generating and maintaining mitochondria

Key Findings

1. **ZnLG Mitigates Deficiency-Related Mitochondrial and Bacterial Outcomes (Figure 1a-c).**

   Zn deficiency induces mitochondrial damage, increases mitochondrial reactive oxygen species (ROS) production, and attenuates bacterial clearance (data not shown). Treatment with ZnLG reduces mitochondrial damage (Fig. 1a), decreases mitochondrial ROS production (Fig. 1b) and improves bacterial clearance (Fig. 1c).

1a. Cell Membrane Integrity | **1b. Phagocytic Uptake** | **1c. Bacterial Killing**

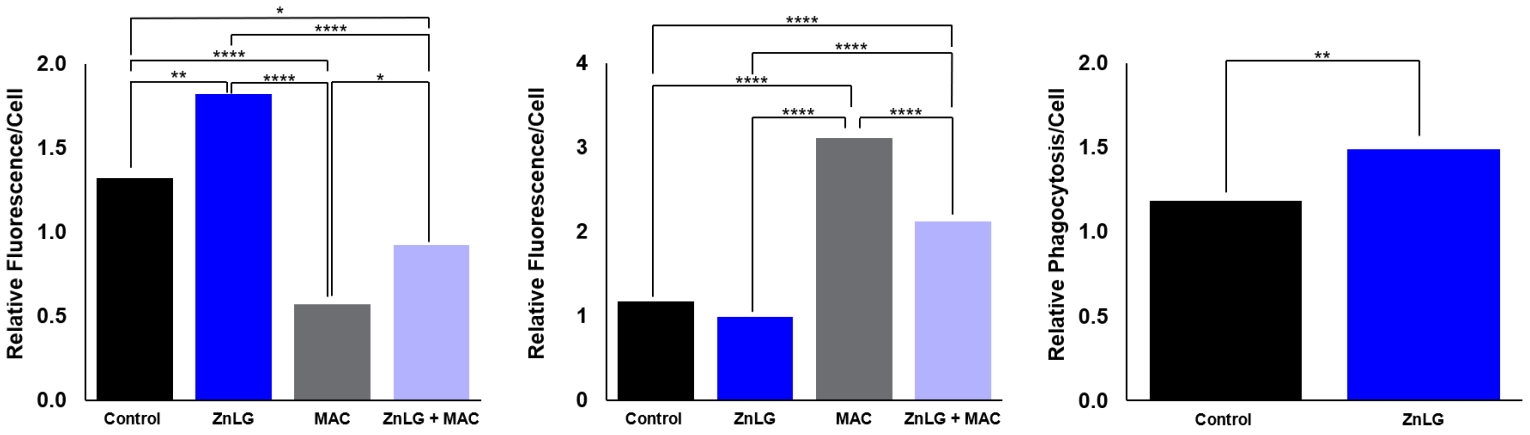


Figure 1a-c. ZnLG Supplementation Improves Mitochondrial and Bacterial Outcomes

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.001$; Data extrapolated from charts in publication

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2. **ZnLG Restores Regulators of Mitochondrial Biogenesis Following MAC Infection (Figure 2a-b).**

   Zn deficiency during MAC infection reduces expression of key transcriptional regulators of mitochondrial biogenesis (data not shown). The ZnLG treatment restores PGC-1α and TFAM expression following MAC infection.

3. **ZnLG Restores Regulators of Mitochondrial Biogenesis Following ZIP8 Loss (Figure 2c-d).**

   ZIP8 loss reduces expression of key transcriptional regulators of mitochondrial biogenesis in response to MAC infection (data not shown). The ZnLG treatment restores PGC-1α and TFAM expression following MAC infection of ZIP8 knockout BMDMs.

4. **ZnLG Improves Macrophage Antibacterial Function Despite ZIP8 Loss (Figure 2e-f).**

   ZIP8 loss enhances MAC-induced mitochondrial damage, increased mitochondrial ROS production, and decreased bacterial clearance (data not shown). Treatment with ZnLG attenuates mitochondrial damage and deficits in macrophage antibacterial activity during MAC infection in ZIP8 knockout macrophages.

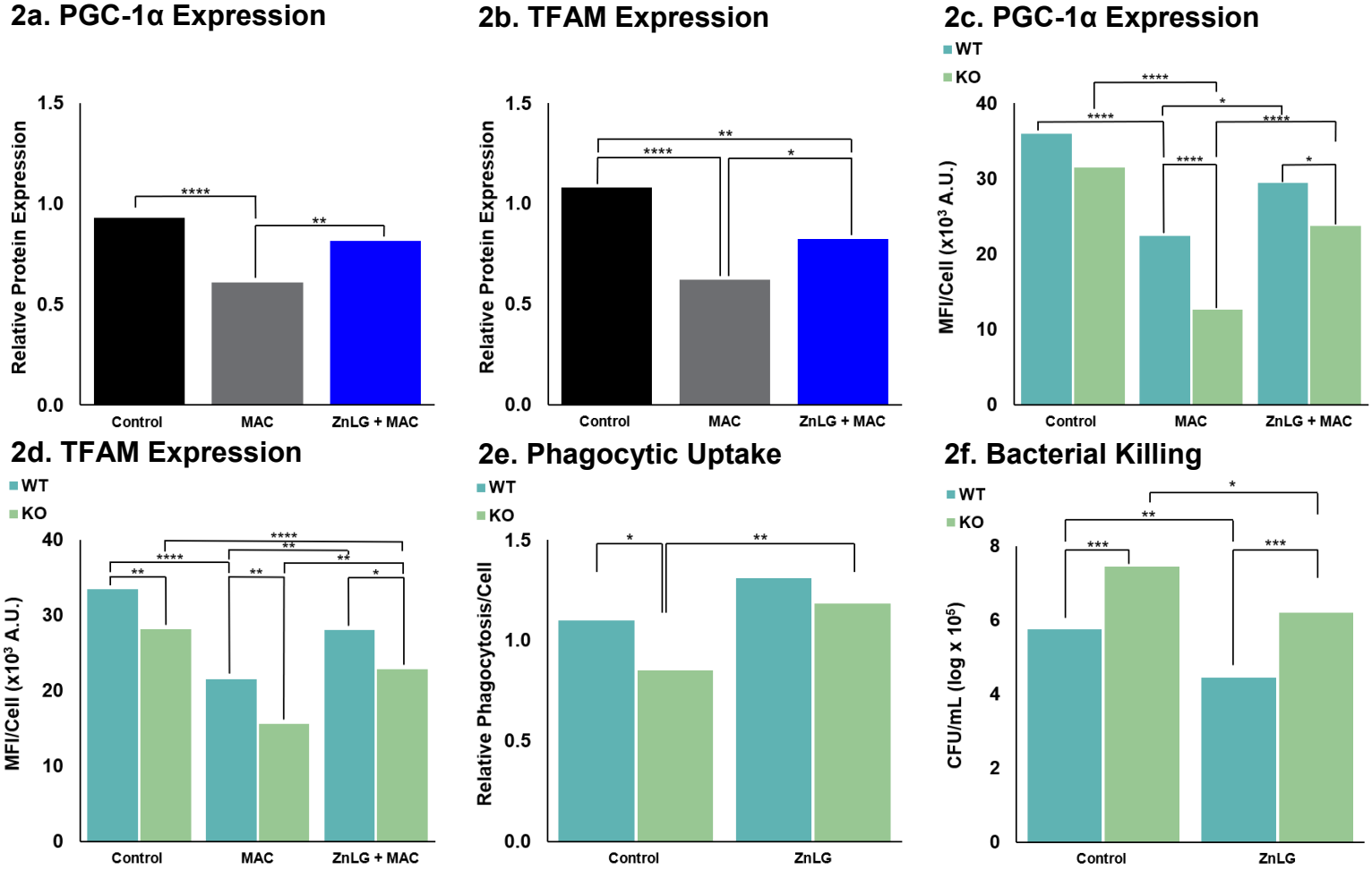


Figure 2a-f. ZnLG Supports Mitochondrial Function and Macrophage Antibacterial Activity

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.001$; Data extrapolated from charts in publication

Conclusion & Implication

Zinc plays a critical role in maintaining mitochondrial function and antibacterial activity in macrophages during MAC infection. Insufficient intracellular Zn reduced expression of key regulators of mitochondrial biogenesis, including PGC-1α and TFAM, resulting in impaired mitochondrial function and bacterial clearance. ZnLG supplementation attenuated these effects by restoring mitochondrial function and improving macrophage antibacterial activity.

These findings highlight the importance of Zn status in supporting mitochondrial health and immune resilience. A highly bioavailable Zn amino acid complex (ZnLG) restored mitochondrial regulators and macrophage function under conditions of Zn deficiency and impaired intracellular Zn transport.

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