Unraveling The Immune Metabolic Epigenetic Axis To Improve TB Therapy

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Background

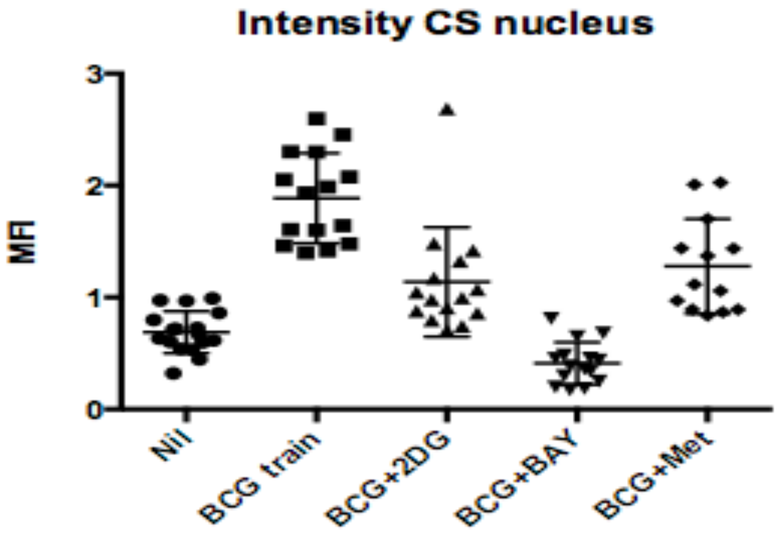
- Tuberculosis (TB) remains a global scourg with 10.4 million cases and 1.5 million deaths a year.
- TB is unique in that despite being culture negative after two months of anti-TB therapy, treatment must be continued for a least six months.
- Studies have shown that Metabolic activation drives epigenetic-mediated immune phenotypes.

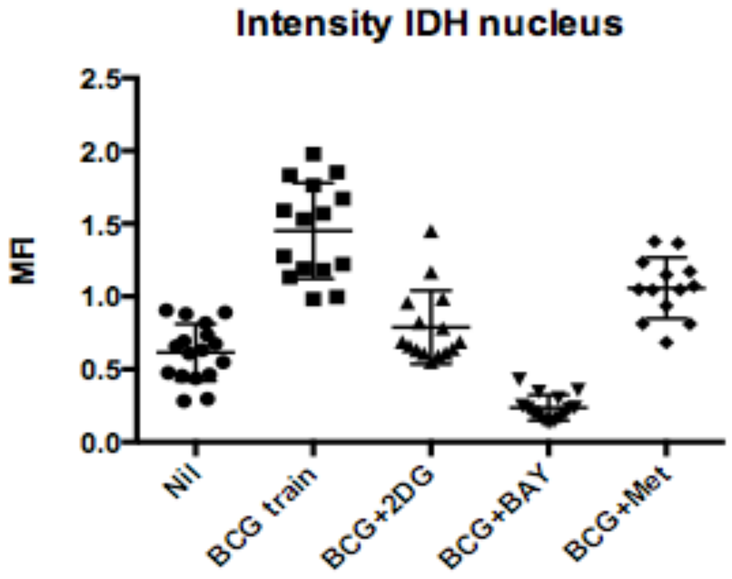
Aims

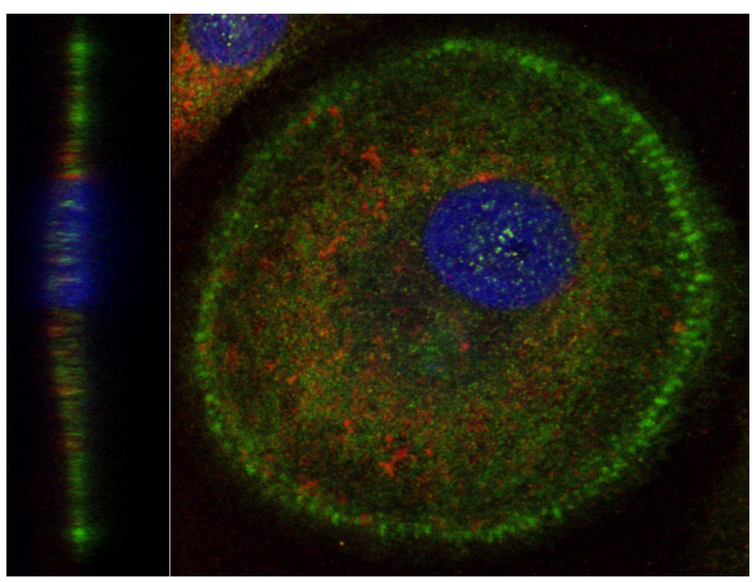
- Identify the metabolic pathways that discriminate beneficial innate immune training and detrimental immune tolerance
- Identify the metabolic pathways that drive epigenetic-mediated immune tolerance.
- Evaluate the capacity of modulating drugs to block or reverse immune tolerance and improve anti-mycobacterial immunity.

Methods

- In vitro assays implemented with monocyte derived macrophages from healthy controls using plastic adhesions. Induced beneficial training using BCG and detrimental tolerance using LPS.
- To clarify metabolic mechanisms that drive tolerance we implemented confocal microscopy, used chemical inhibitors of metabolic pathways and flow spectrometry.







Results

- Trained and tolerant protocols induced TCA moonlighting of IDH3 and CS ($p<0.05$ by Mann-Whitney, n=5)
- Glycolysis, glutaminolysis, mTOR, and NFAT play a critical role in allowing TCA enzymes to moonlight the nucleus.

Conclusion

Moonlighting of TCA enzymes in the nuclei of macrophages plays an important role in driving the immune phenotype. Trained phenotype exhibit an increase in cytokine production, while the tolerant phenotype demonstrate a decrease in cytokine production.

Acknowledgment and funding

This work was supported by Texas Children's Hospital intramural funding.

References

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