

The *M. tuberculosis* F15/LAM4/KZN Strain

is not more virulent than the Globally Prevalent Beijing Strain during Early Infection of Alveolar Macrophages



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Introduction

Previous studies have established that divergent *M. tuberculosis* strains induce strain-specific transcriptional host responses in *M. tuberculosis* infected macrophages at different times post-infection (Koo *et al.*, 2012).

We studied the *in vitro* host macrophage response to early infection by *M. tuberculosis*, gene expression levels of human alveolar macrophage THP-1 cells at 48 hours post-infection with *M. tuberculosis* clinical strains Beijing and F15/LAM4/KZN, and the laboratory strain H37Rv were compared to the relative transcriptome from uninfected THP-1 cells.

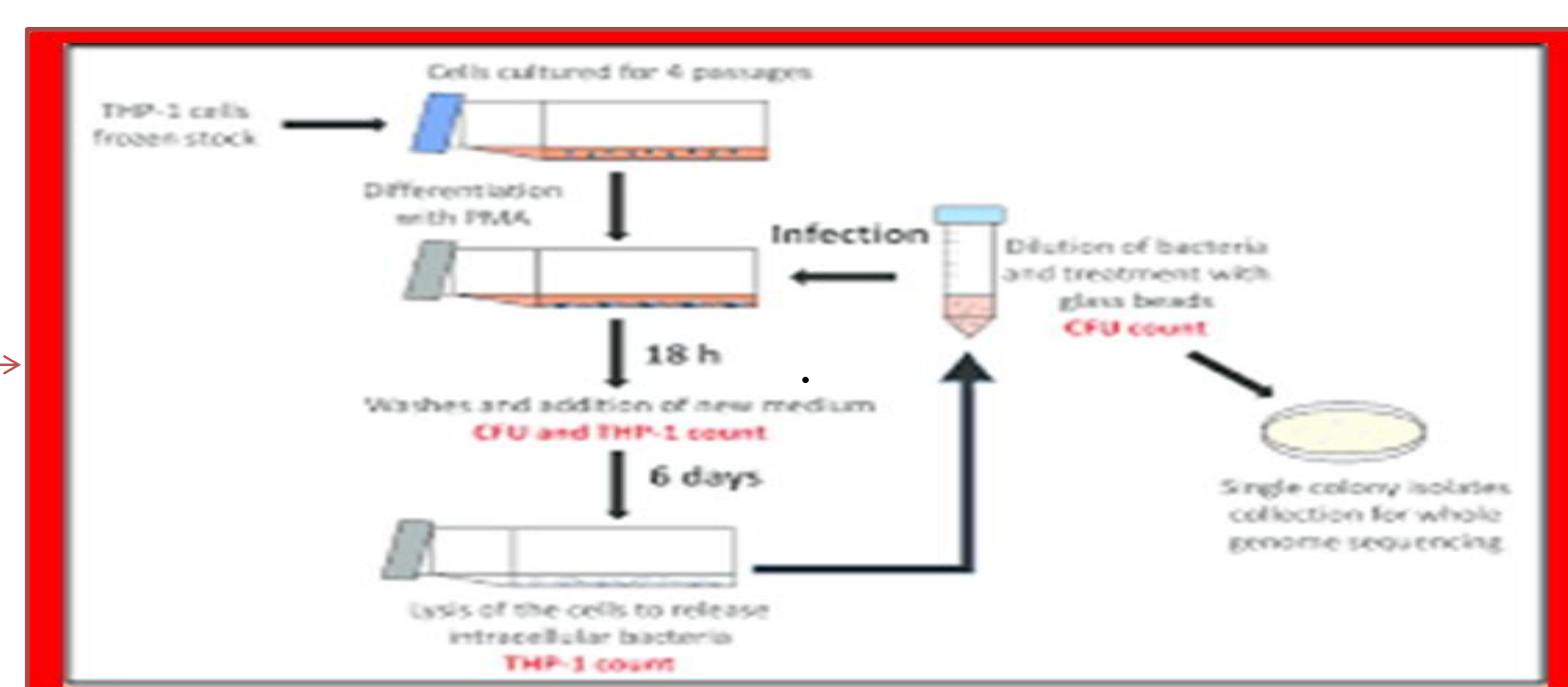
Findings from this study will shed light on macrophage response of F15/LAM4/KZN compared to the globally prevalent and virulent Beijing strain.

Materials and Methods

M. tb strains (Beijing, F15/LAM4/KZN, H37Rv)

Growth in 7H9

Middlebrook 7H9 broth, supplemented with 0.5% (vol/vol) glycerol, 0.05% (vol/vol) Tween-80 and 10% (vol/vol) Oleic Acid Albumin Dextrose Catalase (OADC)



Cytokine and Chemokine analysis

Macrophage RNA harvesting and extraction from infected and uninfected THP-1 cells 48hpi.

RNA-Sequencing and data analysis:

1. Preprocessing (FastQC, Trimmomatic)
2. Mapping (HISAT2 mapping manager)
3. Transcript assembly (StringTie)
4. Functional enrichment

Results

We elucidated macrophage response through gene expression patterns, molecular signatures and cytokine response in pulmonary alveolar macrophages during early infection with Beijing and F15/LAM4/KZN clinical strains of *M. tuberculosis* that dominate in the KwaZulu-Natal province of South Africa. Insight on the ability of the strains to stimulate early host immune responses that can be implicated to the transmission dynamics of these strains in the South African population.

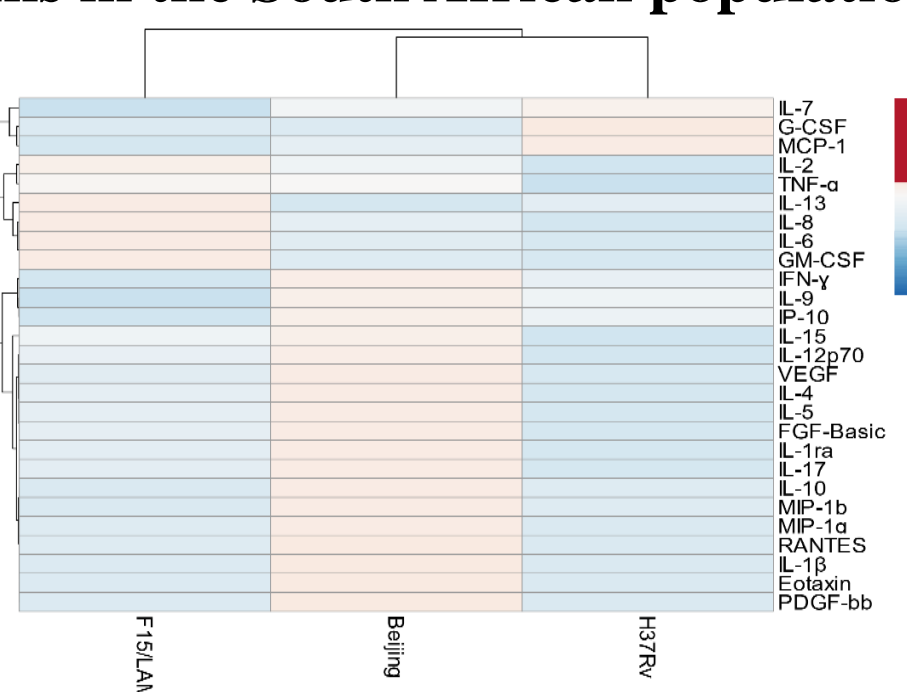


Figure 1: Heat map and hierarchical cluster analysis comparing fold-changes of cytokine/chemokine production by THP-1 macrophage cells infected by the Beijing, F15/LAM4/KZN, and H37Rv strains of *M. tuberculosis* at 48 hours interval.

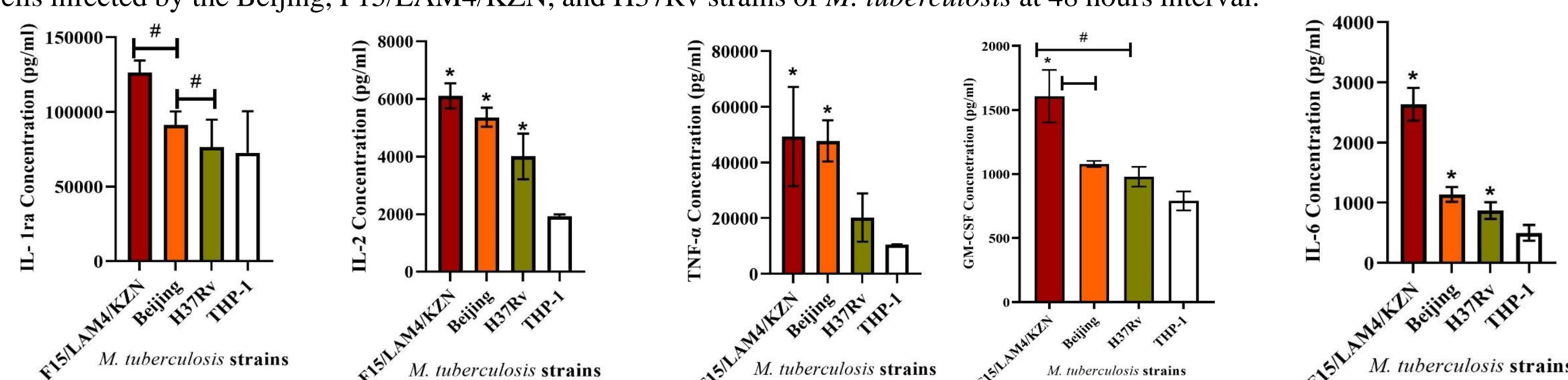


Figure 2: Strain-specific cytokines induced at 48-hours post-infection of uninfected and infected THP-1 macrophage cells with *M. tuberculosis* strains F15/LAM4/KZN, Beijing, and H37Rv.

Results

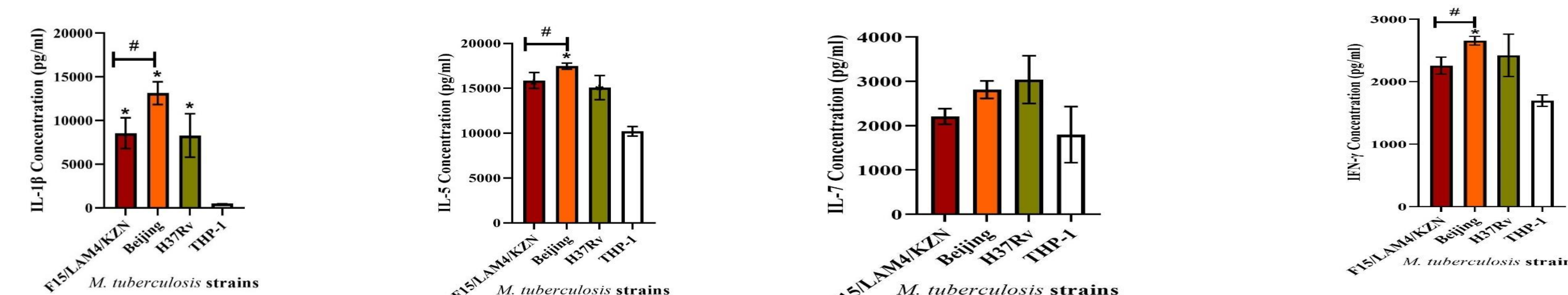


Figure 3: Strain-specific anti-inflammatory cytokines induced at 48-hours post-infection of uninfected and infected THP-1 macrophage cells with *M. tuberculosis* strains F15/LAM4/KZN, Beijing, and H37Rv.

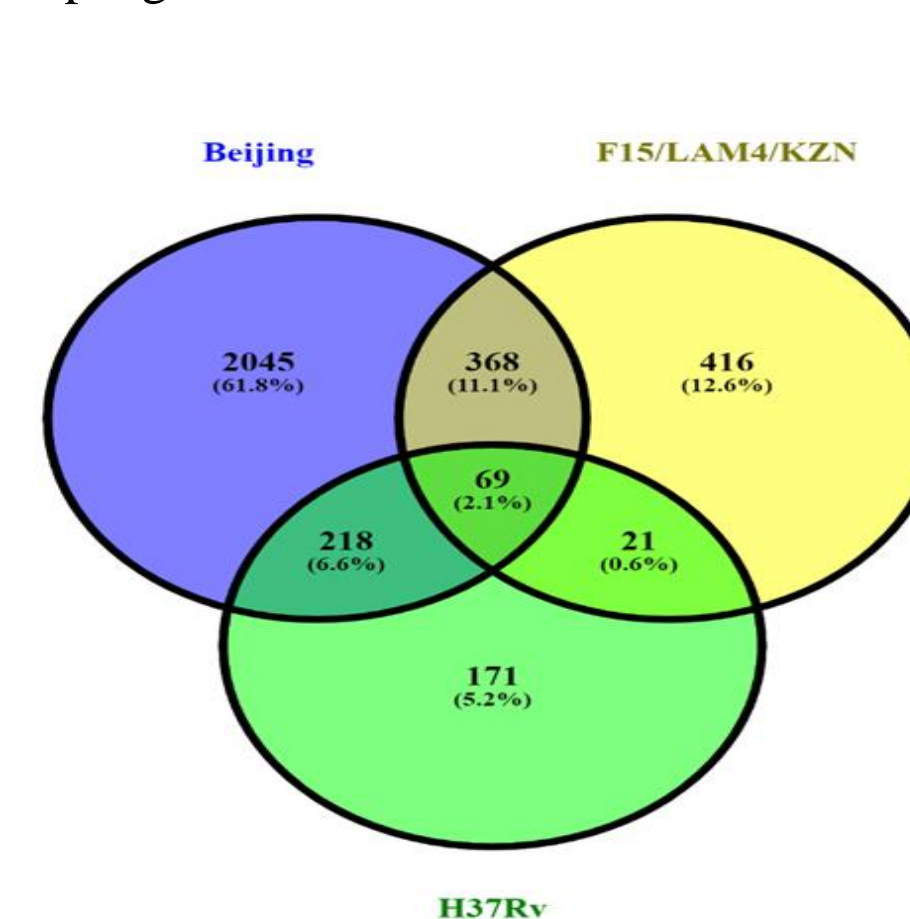


Figure 4: Total number of significant differentially expressed genes (SDEGs) at 48 hours post-infection by Beijing-, F15/LAM4/KZN, and the H37Rv laboratory strain, relative to the uninfected host cell.

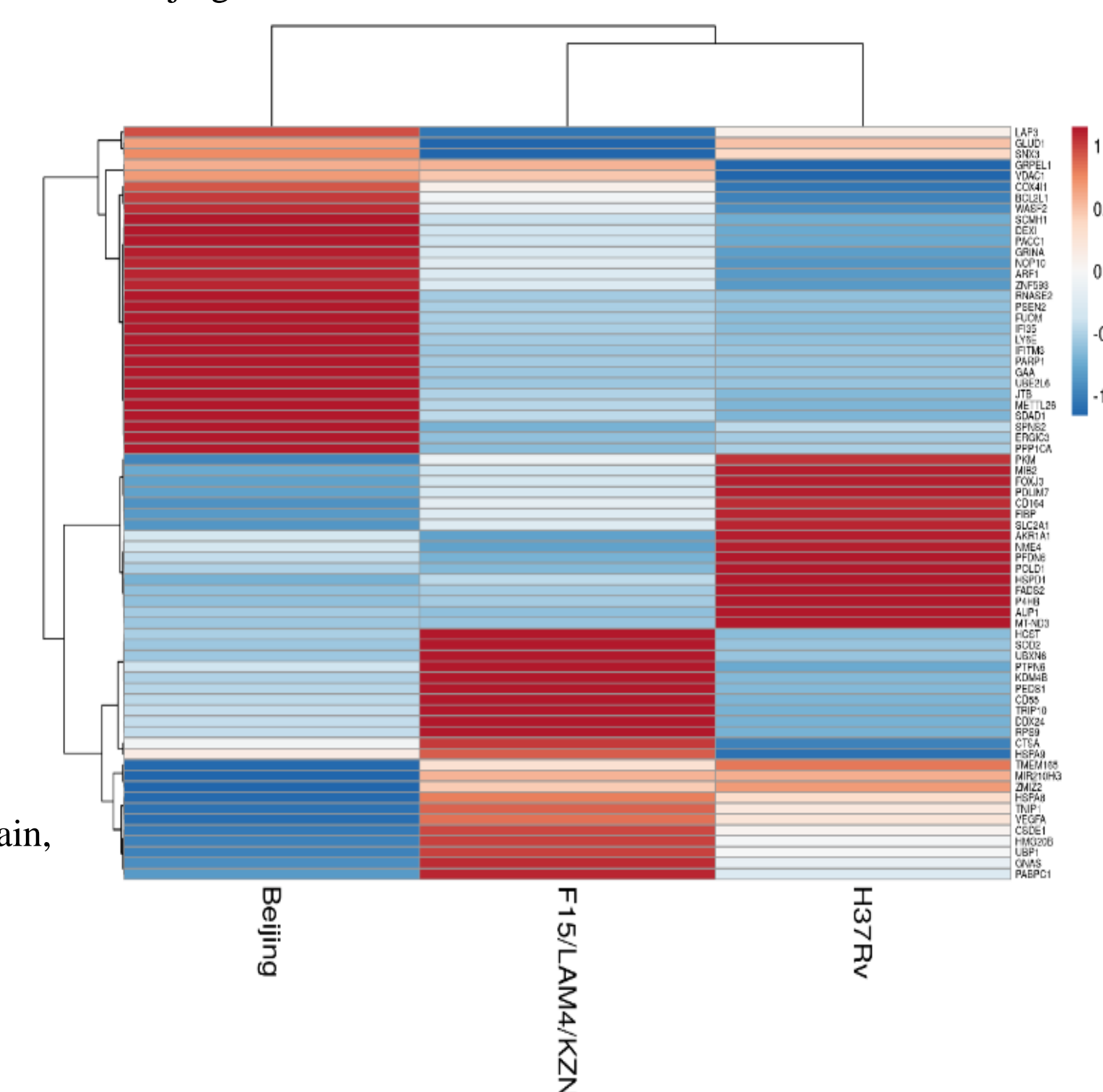


Figure 5: Differential gene expression patterns of commonly induced SDEGs in THP-1 macrophage cells at 48 hours post-infection with the Beijing, F15/LAM4/KZN, and H37Rv *M. tuberculosis* strains.

Strain-specific response of alveolar macrophages to genetically diverse clinical strains of *M. tuberculosis*, which alludes to the presence of specific virulence determinants within the Beijing, F15/LAM4/KZN, and H37Rv strains.

Discussion and Conclusions

We have compared, for the first time, alveolar macrophage transcriptional responses to infection with clinical *M. tuberculosis* strains from distinct MTBC lineages 48 hours post infection.

Differences in the expression profiles of SDEGs suggest that there are complex and dynamic host-pathogen interactions taking place during infection by clinical strains of *M. tuberculosis* compared to laboratory strain that may potentially influence host protection or disease pathogenesis.

F15/LAM4/KZN is not more virulent than the globally prevalent Beijing strain.

Hence, the high transmission dynamics of this strain in the Tugela ferry outbreak may be linked to the drug resistance patterns within this strain family and other health care system challenges in South Africa; and not failure to activate macrophages during early infection.

Lastly, from our observations and those from previous studies we conclude that various factors, such as host genotype, and the bacterial strain, play a significant role in the host response to infection.

References

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