Reviewer’s report

Title: Differential expression of M. tuberculosis-induced Suppressor of Cytokine signaling (SOCS) 1 and 3 and FoxP3 molecules linked with variable cytokine profiles is associated with clinical severity of tuberculosis

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Reviewer: Adrian Martineau

Reviewer’s report:

This manuscript compares expression of a modest number of candidate genes in healthy TST-negative controls vs. patients with tuberculosis of varying severity at various different body sites.

Major

1. A modest number of candidate genes is investigated – inevitably the amount of information acquired is limited in comparison with recent studies that take a genome-wide approach to identifying genes whose expression differs between patients with disease at different sites vs controls.

2. Study participants are categorised into many different sub-groups, each of them small – consequently it is hard to interpret the numerous associations reported. This sub-division also introduces potential for type I error to creep in – but no adjustment has been made for multiple analyses. Either the number of sub-group analyses should be reduced, or an adjustment for multiple analyses should be applied.

3. The abstract concludes that expression of SOCS1 and SOCS3 impact on Th1/Th2 balance, which in turn determine outcome of infection – but to infer this sequence of cause and effect on the basis of cross-sectional associations is to go beyond the data. The differences in gene expression patterns seen in patients with moderate vs severe disease could be a cause or a consequence of disease severity, for example.

Minor

1. Title: I had to read this a few times to get my head around it – is it possible to simplify the title to convey the key message? One suggestion: Expression of M. tuberculosis-induced Suppressor of Cytokine signalling (SOCS) 1 and 3 and FoxP3 associates with clinical severity of tuberculosis

2. Abstract: Background: ‘IFN-gamma is lowered in tuberculosis (TB)’ – does this statement refer to circulating levels, antigen-stimulated levels, gene expression or other? Wording should make this explicit

3. The abstract contains numerous unconventional abbreviations (e.g. L-ETB, D-ETB), which make it difficult to interpret the Results section readily

4. Introduction: ‘CD4+ T cells play a central role in containment of M. tuberculosis infection by secreting Interferon-gamma (IFN- ), IL12 and TNF’ – IL12 and TNF
are primarily secreted by macrophages rather than CD4+ cells

5. Methods – a single 18h time point was employed for assays of gene expression and cytokine secretion. However, antigen-stimulated IFN-gamma may not reach peak concentrations until 72h or later post-stimulation. Were timecourse experiments conducted to justify selection of this single timepoint? If not, then this needs to be noted as a study limitation.

6. Table 1 seems to list characteristics of study participants rather than ‘diagnostic criteria’ – these should appear at the beginning of results, rather than in Methods as they do presently

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests