Correspondence

Reply to Eisenhut

To the Editor—We recently reported that individuals with high exposure to tuberculosis, including latent tuberculosis infection (hE), display higher ex vivo interferon-\(\gamma\) (IFN-\(\gamma\)) responses (percentage of IFN-\(\gamma\)-producing tuberculin-induced CD4 T cells) than do patients with active pulmonary tuberculosis [1]. In fact, the percentage of ex vivo tuberculin-inducible CD4 T cells was generally higher in hE when activation was defined as upregulation of \(\geq 1\) marker out of a panel of 5 activation markers, CD40L, degranulation (CD107 mobilization), IFN-\(\gamma\), interleukin-2, and tumor necrosis factor \(\alpha\).

In his letter, Eisenhut proposes an explanation for our observation [2]. He argues that the decrease of IFN-\(\gamma\)-producing T cells in active pulmonary tuberculosis may be the result of...
active suppression, resulting from overexpression of suppressor of cytokine signaling genes in the lung that impair T helper 1 immunity. He further suggests that anergy (reflected by negative tuberculin skin test [TST] results) in some of our active pulmonary tuberculosis patients may have contributed to lower percentages of IFN-γ-producing T cells in this group.

We fully agree that, in light of recent (and indeed older) publications, an active suppressive mechanism might explain a reduction in IFN-γ-producing T cells in the active pulmonary tuberculosis group and that this may occur as a result of T regulatory cell (Treg) induction by tuberculosis antigens [3–5]. Unfortunately, our study did not include any markers that would allow us to identify Treg populations.

Interestingly, however, we found no correlation between the numbers of tuberculin-activated IFN-γ–producing CD4 T cells ex vivo and the size of the reported TST result in millimeters within this group. Of note, the TST in this study usually preceded the beginning of therapy, whereas we examined patients up to several weeks into therapy, so that a relevant comparison (ie, both tests at the same time) cannot be made. We are not aware of a study in which the TST was applied and blood for ex vivo tuberculin stimulation followed by intracellular cytokine staining was obtained at the same time. Such a study would be very interesting.

It is important to note that a positive response to tuberculin in the skin test will depend on dendritic cell function in the skin and successful migration of T cells to the site of tuberculin application apart from T-cell reactivity per se. This involves a range of different factors that are simply bypassed in the ex vivo blood test [6, 7]. A recent Mycobacterium bovis outbreak in cattle in the UK resulted in positive IFN-γ test results but complete skin test anergy [8]. Such phenomena are not well understood at this time, but the observation seems to caution against the conclusion that skin anergy is indicative of a general nonreactivity of the cellular immune system.

Importantly, our report has shown that cellular markers other that IFN-γ may be helpful in discriminating between high-exposure/latent tuberculosis infection and acute tuberculosis—in particular, that the functional profile of T cells changes as control over the infection is lost. Whether this change of profile results from the action of Tregs remains to be studied.

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Reference


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