

## Morphological modification by tubercle bacilli: no time for denial

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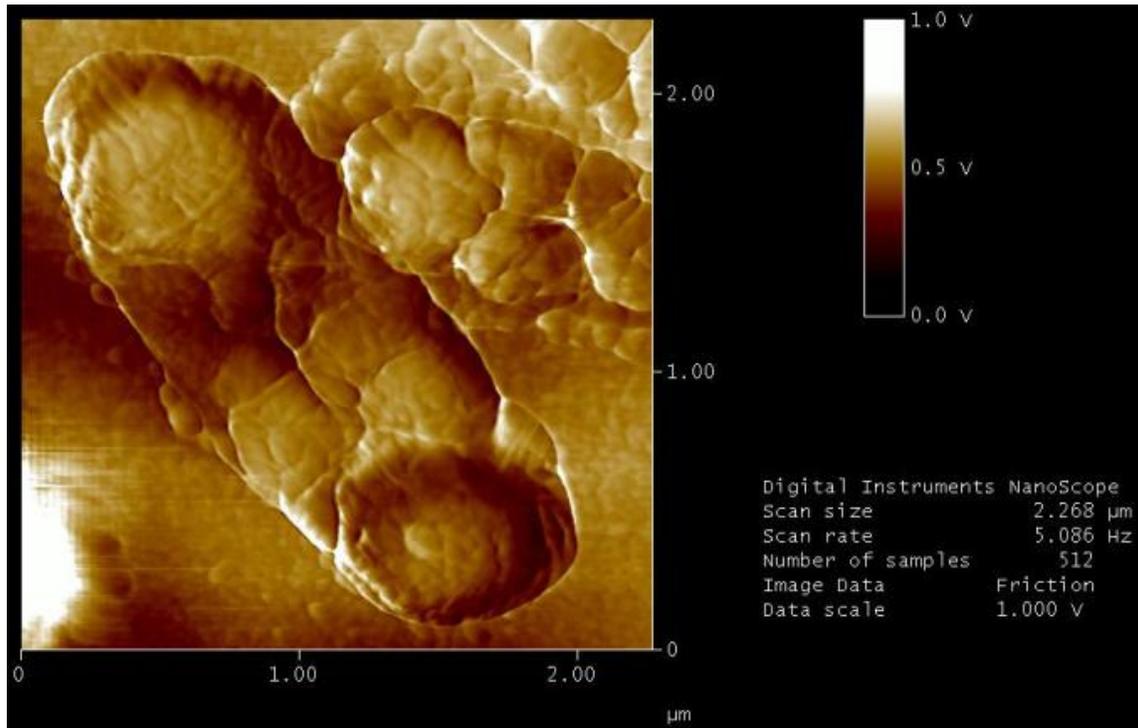
To be very honest, few people care about bacterial morphology. This is very unfortunate, because the subject of morphology addresses a fundamental biological question, the significance of which has been decided by the organisms themselves. A simple way to verify this is to take a look at the cultures of *M. tuberculosis* under different condition inside and outside the host [1]. They become shorter in older cultures, filamentous within macrophages, and ovoid during starvation [2,3]. These morphological changes are examples in which cell shape is implicated but not yet proven to be important. Based on World Health Organization (WHO) data, there are 8 million active cases of tuberculosis (TB) with 3 million deaths per year. In addition, about one third of the global population is estimated to suffer from latent tuberculosis [4]. This high number of cases may not only reflect the poor implementation of TB control programs, but it may also represent our failure to understand the basic biology of *M. tuberculosis*.

We recently demonstrated the morphological changes in extremely drug-resistant (XXDR) tuberculosis strains [5,6,7]. The XXDR-TB strains showed *in vitro* resistance to all first- and second-line drugs tested [8,9]. Under atomic force microscopy, 30% of the XXDR-TB cells had an oval- or round-shaped appearance [5,6]. In this context, Champion and Mitragotri highlighted the

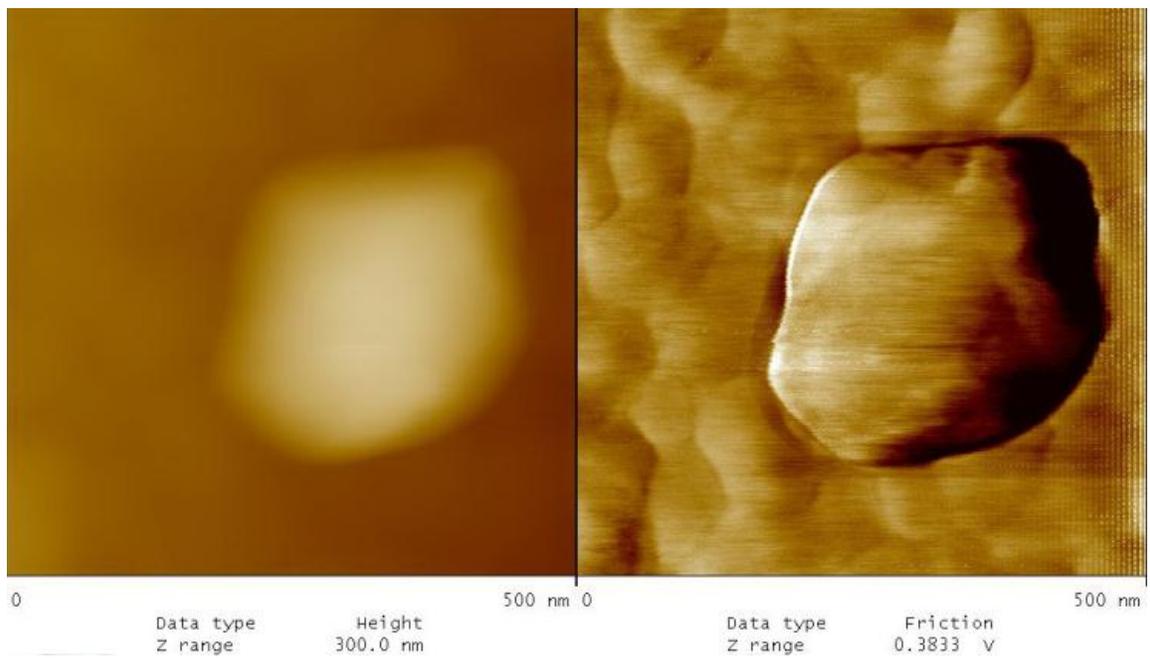
importance of morphology with regard to the immune system [10]. Those authors created microscopic polystyrene particles of six different shapes in various size, fed them to alveolar macrophages, and found that shape, not size, was the dominant factor in determining whether particles were phagocytized [10]. Thereby, morphological alterations in XXDR-TB strains, could explain the enhanced ability of bacilli to escape immune responses [7]. At present, the numbers of patients infected with XXDR-TB strains are low, but the main problem is how to cure and control such cases without effective antibiotics and new preventive strategies, respectively. More recently, we studied the anaerobic culture of *M. tuberculosis* as a model of latency [11]. For the first time, the sequential changes in tubercle bacilli (H<sub>37</sub>RV) from one month to 48 months of latency were documented. The latent TB bacilli transformed themselves from classical rod-shaped, acid-fast cells (1.5 to 3.0 µm size) into oval and non acid-fast forms (0.1 to 0.3µm). These cells were metabolically active and they could recover their original biological properties when they transferred into a favorable environment (mice model). Therefore, TB bacilli can adapt and survive in any hostile environment by changing its morphology (Figures 1 and 2).

In conclusion, shape of bacilli can be seen as a marker of virulence, of biological defense against

**Figure 1.** Laboratory strains of *M. tuberculosis* (H37RV) at exponential phase of growth. Viewed under atomic force microscopy (AFM)



**Figure 2.** Latent *M. tuberculosis* (H37RV) after 36 months of anaerobic culture. The latent TB bacilli are ovoid and are non acid-fast forms (0.1 to 0.3 $\mu\text{m}$ )



specific immune responses, or of cell division. Today, most of investigators agree that the Koch bacillus does not always manifest itself in the classical rod shape. However, the possible significance of such variant forms with respect to etiology, control, and prognosis of tuberculosis infection are not very clear. Hence the efforts to design new strategies and innovative approaches should target these uncharacterized cell populations of *M. tuberculosis* also. This is an urgent issue that needs support from the global scientific community.

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