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EDITORIAL

Trick or tween: An inflammatory surprise when *M. tuberculosis* knocks a cell's door and no tween is provided

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Mycobacterium tuberculosis causes tuberculosis and 1.4 million related deaths in 2015. 10.4 million new cases of tuberculosis were reported in 2015 alone (56% men, 34% women and 10% children).[1] Transmission of *M. tuberculosis* occurs when bacteria-laden cavity has eroded into bronchial airways through which bacteria can be coughed out into the air. Pulmonary cavitation usually takes place in immunocompetent adults, not in children or immunocompromised HIV-infected persons. It is a result of chronic inflammation and is associated with the degree of delayed-type hypersensitivity response in the infected persons.[2] Understanding how such inflammatory response is generated by *M. tuberculosis* is therefore crucial to design strategies to interrupt the pathogenesis and transmission of tuberculosis. One way toward this goal is to examine the initial responses to *M. tuberculosis* infection in macrophage, which is the first host immune cell that encounters the bacterium.

In this issue of *Virulence*, Leisching et al. compare the transcriptional responses of human macrophages to 2 well-characterized clinical strains.[3] The 2 strains have a similar genetic background but differ in the transmission capability. Both strains are isolated from patients during outbreaks of tuberculosis transmission.[4] The hypervirulent strain is epidemiologically associated with increased ability to cause disease and spread in comparison to the hypovirulent strain. The authors reveal a profound pro-inflammatory transcriptional profile caused by the hypervirulent strain when compared against the hypovirulent strain. Indeed, the hypervirulent strain induces significantly higher secretion of proinflammatory cytokines TNF-α, IL-1beta and IL-6 but similar secretion of anti-inflammatory cytokine IL-10.

The high-resolution transcriptional analysis RNAseq performed by Leisching et al provides additional information of the proinflammatory nature of the hypervirulent *M. tuberculosis*.[3] It reveals an upregulation of the DNA damage Gadd45 signaling pathway, whose role in tuberculosis remains largely unknown. Two host defenses oasl1 and slpi are highly induced as well. Oasl1 is a negative regulator of type I interferon production.[5] Slpi is a negative regulator of host response toward inflammatory lipopolysaccharide[6] and inhibits generation of neutrophil extracellular trap.[7] Induction of type I interferon production and formation of neutrophil extracellular trap have been observed from patient with tuberculosis.[8,9] Thus, what the RNAseq analysis has revealed may represent attempts by host cells to restrain further pathological outcome when being challenged with the proinflammatory effect of a hypervirulent *M. tuberculosis* strain.

The result of Leisching et al on the proinflammatory nature of the virulent isolates of *M. tuberculosis*, however, is not consistent with the results from previous studies. Instead, those studies indicate that virulence of *M. tuberculosis* is associated with low inflammatory responses. *M. tuberculosis* Beijing sublineage strain is associated with increased virulence and transmission.[10] A hypervirulent Beijing family strain produces a phenolic glycolipid that inhibits secretion of pro-inflammatory cytokines.[11] Modern lineages including the Beijing sublineage are associated with rapid disease progression and transmission and have lower inflammatory phenotypes when compared with ancient lineages.[12-14] What could be the reason behind the difference between these studies and the present study by Leschieng et al.?

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Comment on Leisching G, et al. RNAseq reveals hypervirulence-specific host responses to *M. tuberculosis* infection. Virulence 2017; 8(6):848-858; PMID:27763806; https://doi.org/10.1080/21505594.2016.1250994

The same research group of the present study has recently reported that *M. tuberculosis* grown without Tween 80 produces proinflammatory phenotypes but when grown with Tween 80 produces anti-inflammatory phenotypes.[15] Tween 80 is a detergent commonly added into the growth medium of *M. tuberculosis* to prevent clumping, which prevents accurate determination of the ratio of the infecting bacteria number to the number of targeted host cells. Therefore, it is a common practice to include Tween 80 when preparing *M. tuberculosis* for infections, which was the case in all previous transcriptional response studies. The authors suggest that Tween 80 strips off lipids and proteins associated on the surface of *M. tuberculosis* that could serve as proinflammatory ligands via host receptors including TLR2, mannose receptor, mincle receptor and dectin-1 receptor.[16] These tween-sensitive ligands include trehalose dimycolate (TDM), mannose-capped lipoarabinomannan and arabinomannan,[16] all of which are virulent.

Further characterization of the proinflammatory characteristic of virulent *M. tuberculosis* should provide new insights into how hypervirulent *M. tuberculosis* can use those tween-sensitive immunostimulatory ligands to initiate and maintain host immune responses such as delayed-type hypersensitivity that promote transmission and disease progression into cavitation in the lung. Efforts to identify components of the underlying pathways may reveal potential targets for host-directed therapy that aims to interrupt disease progression and transmission of tuberculosis.

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