Tuberculosis -- hiding in plain sight

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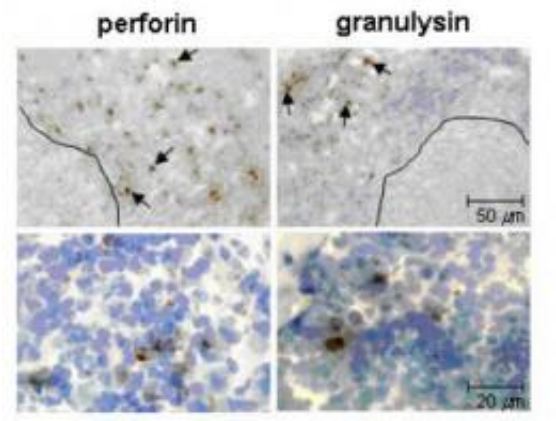

Low levels of the anti-TB effector molecules perforin and granulysin in the granulomas (sold line) of a human TB-infected lymph node. Note the granular and polarized expression of the cytolytic effector molecules in cells located outside the lesions. Credit: Rahman et al, 2009

Current research suggests that Mycobacterium tuberculosis can evade the immune response. The related report by Rahman et al, "Compartmentalization of immune responses in human tuberculosis: few CD8+ effector T cells but elevated levels of FoxP3+ regulatory T cells in the granulomatous lesions," appears in the June 2009 issue of The *American Journal of Pathology*.

More than two million people worldwide die from tuberculosis infection every year. Due in part to inappropriate antibiotic usage, there are a rising number (0.5 million in 2007) of cases of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) tuberculosis. New

therapies are needed to treat these dangerous infections.

Immune responses to tuberculosis rarely result in complete eradication of the infection. Instead, TB-infected immune cells promote the generation of chronic inflammation and the formation of granulomas, which are areas where the bacteria are contained but not destroyed. A group led by Dr. Susanna Grundstrom Brighenti at the Karolinska Institutet in Stockholm, Sweden therefore examined the immune response in patients infected with tuberculosis. This is the first study describing the immunoregulatory mechanism associated with the development of clinical disease at the site of infection in human TB. They found that while the immune cells responsible for killing the tuberculosis bacteria surrounded the granuloma, these cells had low levels of the molecules necessary to kill the TB. Instead, granulomas had high numbers of regulatory immune cells. These regulatory cells suppress the immune response, resulting in the survival of the tuberculosis bacteria and perhaps contributing to persistent long-term infection.

This study by Rahman et al "provide[s] evidence that the adaptive immune response in establishment of clinical TB [is] skewed towards a suppressive or regulatory phenotype that may inhibit proper immune activation and down-regulate the host response at the local site of infection. Compartmentalization of the immune response in human TB could be part of the reason why infection is never completely eradicated but instead develops into a chronic disease." In future studies, Dr. Grundstrom Brighenti and colleagues plan to "pursue new strategies developed to enhance cell-mediated immune responses that are known to provide protective immunity in patients with TB. Such an approach may involve targeting of certain subpopulations of immune cells with anti-inflammatory or immunoregulatory properties."

More information: Rahman S, Gudetta B, Fink J, Granath A, Ashenafi

S, Aseffa A, Derbew M, Svensson M, Andersson J, Grundstrom Brighenti: Compartmentalization of immune responses in human tuberculosis: few CD8+ effector T cells but elevated levels of FoxP3+ regulatory T cells in the granulomatous lesions. *Am J Pathol* 2009 174: 2211-2224

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