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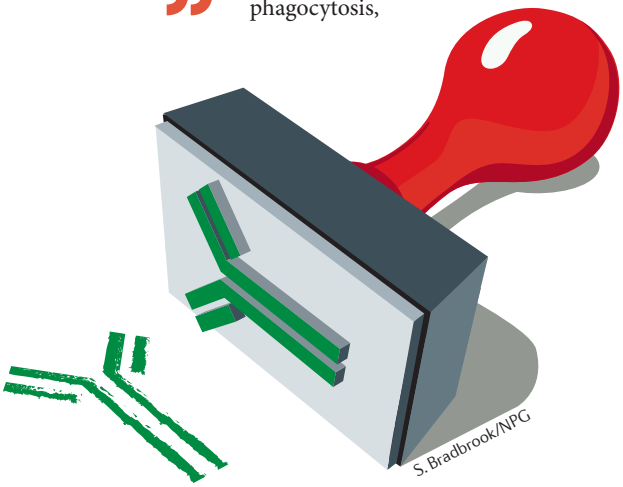
ANTIBODIES

Marking disease states in tuberculosis

Cellular immunity is important for protection against *Mycobacterium tuberculosis* infection, but the role of humoral immunity has been unclear. Now, Alter, Fortune and co-workers show that individuals with latent and active tuberculosis (TB) infection have different antibody profiles with distinct antibody glycosylation patterns. Antibodies in latent TB infection have enhanced Fc-dependent effector profiles and can activate macrophages to kill intracellular bacteria.

> antibodies from patients with latent TB can activate antimicrobial responses

To investigate the role of humoral immunity in TB disease, the authors analysed plasma-derived IgG from individuals with latent or active TB. They assessed 70 features, including the ability of IgG to induce antibody-dependent phagocytosis, antibody-dependent cellular cytotoxicity, IgG binding to activating and inhibitory Fc receptors (FcRs) and IgG glycosylation. Principal-component analysis of the antibody features identified nine features that distinguish the humoral profiles of latent and active TB, and differential antibody glycosylation was one of the main features. Further analysis identified distinct profiles of Fc effector functions; for example, IgG from individuals with latent TB were associated with increased antibody-dependent cellular cytotoxicity and activation of natural killer (NK) cells. Furthermore, IgG from individuals with latent TB showed increased binding to the activating FcγRIII, which is known to drive NK cell activation and antibody-dependent cellular cytotoxicity. Thus, individuals with latent and active TB show distinct antibody signatures and Fc effector functions.



Next, the authors examined whether the divergent functional profiles could be due to differences in antibody glycosylation. Capillary electrophoresis showed that the IgG glycan profiles from latent and active TB clustered in distinct groups. Of note, there were striking differences in terms of the levels of galactose and sialic acid, which are known to be associated with inflammation. IgG from individuals with latent TB had fewer inflammatory agalactosylated structures and more anti-inflammatory digalactosylated structures as well as higher levels of anti-inflammatory sialic acid compared with IgG from individuals with active TB. Removing the glycans from purified IgG reduced antibody-dependent cellular phagocytosis. Hence, individuals with latent and active TB have distinct antibody glycosylation profiles that drive antibody effector functions.

So, can antibodies contribute to control of *M. tuberculosis* infection? The authors found that pooled IgG from latent TB infections, compared with active TB infections, increased inflammasome activation and co-localization of *M. tuberculosis* with lysosomes in TB-infected human monocyte-derived macrophages, which is important for control of intracellular bacterial infections. Furthermore, treatment of *M. tuberculosis*-infected macrophages with IgG from latent TB infections decreased the bacterial load by promoting the ability of macrophages to kill bacteria. Thus, antibodies from patients with latent TB can activate antimicrobial responses more effectively than antibodies from patients with active TB infections.

These data support a role for antibodies in the immune response to *M. tuberculosis* infection and suggest that the antibody profiles could be used as biomarkers to distinguish latent from active TB infection.

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ORIGINAL ARTICLE Lu, L. L, *et al.* A functional role for antibodies in tuberculosis. *Cell* **167**, 433–443 (2016)