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BACTERIAL PATHOGENESIS

Getting all tangled up

Mycobacterium abscessus is a nontuberculous mycobacterium that is commonly found in the environment and is responsible for healthcare-associated infections, such as pulmonary infections in patients with cystic fibrosis, but also in immunocompetent individuals. The intrinsic resistance of this rapidly growing mycobacterial species to antibiotics is of major public health concern. *M. abscessus* transitions from a non-virulent smooth morphotype to a virulent rough morphotype that is associated with more severe clinical symptoms in humans. The rough variant forms extracellular cords, which promote unrestricted bacterial growth and have been proposed to be important virulence factors. However, the mechanisms that underlie cording and its role in the pathophysiology of this mycobacterial species are not well understood. In this study, Halloum *et al.* identify a crucial role for an *M. abscessus* dehydratase in cording and pathogenicity.

It was previously shown that deletion of *hadC* in *Mycobacterium tuberculosis*, which encodes a component of the type II fatty acid synthase complex, attenuates virulence and results in a loss of cording. The authors of this study set out to characterize *M. abscessus MAB_4780*, which encodes a dehydratase that is distinct from HadC, by generating the first deletion mutant in the *M. abscessus* rough variant background (Δ*MAB_4780*). They reported that *M. abscessus* lacking MAB_4780 had decreased levels of α-mycolic acid (a lipid component of the mycobacterial cell envelope), which suggests that MAB_4780 has a role in cell wall-associated mycolic acid metabolism by functioning as a dehydratase. MAB_4780-deficient bacteria failed to produce the prominent cords that are formed by wild-type *M. abscessus*. Moreover, the mutant strain displayed increased susceptibility to the antitubercular drug thiacetazone compared with the wild type.

Next, zebrafish embryos were infected with the mutant strain, the wild-type rough variant or the non-virulent smooth variant, and the authors found that whereas the rough variant induced lethal infection, the mutant strain was highly attenuated at a level similar to the smooth variant. In addition, zebrafish embryos that were infected with the wild-type rough variant exhibited massive abscesses and cords, whereas fish that were infected with the mutant had a lower bacterial burden, only a few infectious foci and no apparent cords. The growth of the mutant was also impaired in macrophages compared with the wild-type rough variant, and Δ*MAB_4780* strains failed to induce the formation of granulomas in infected embryos, which is a hallmark of mycobacterial infections. The study also found that MAB_4780 has a role in preventing phagosome–lysosome fusion, a key strategy that is used by pathogenic mycobacteria to avoid exposure to lysosomal hydrolases, thus promoting survival.

Finally, the authors showed that the Δ*MAB_4780* strain remained attenuated in embryos in which either macrophages or neutrophils were depleted. By contrast, these immunocompromised embryos were highly susceptible to infection with the rough variant. The authors hypothesized that following apoptosis of infected cells, bacteria are released and start to form extracellular cords, which, owing to their larger size, might prevent wild-type *M. abscessus* from being phagocytosed by macrophages and neutrophils, and that MAB_4780-deficient strains that have impaired cording are thus more susceptible to clearance by the host immune system.

In summary, the results of this study show that deletion of MAB_4780 attenuates *M. abscessus* pathogenicity owing to decreased cord formation and intracellular growth impairment. Targeting this dehydratase may provide a novel therapeutic strategy to control infection with *M. abscessus*.

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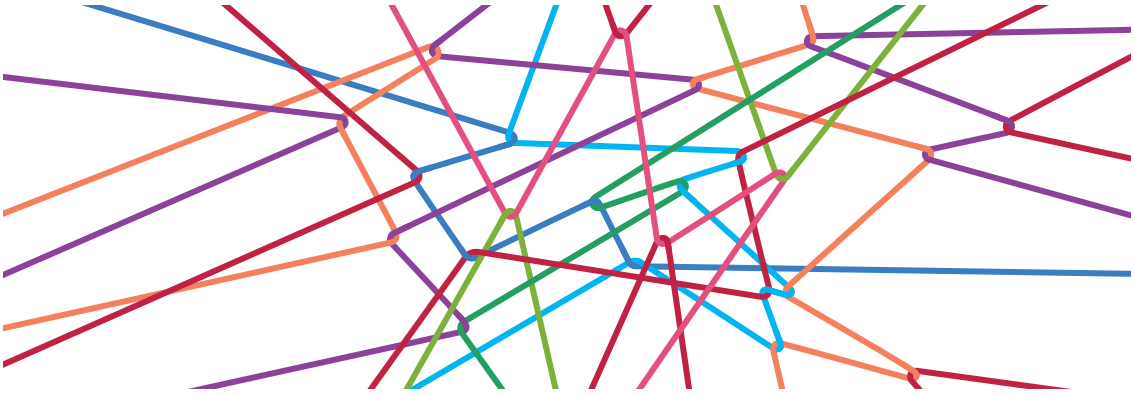
> “MAB_4780-deficient strains that have impaired cording are thus more susceptible to clearance by the immune system”

ORIGINAL ARTICLE Halloum, I. *et al.* Deletion of a dehydratase important for intracellular growth and cording renders rough *Mycobacterium abscessus* avirulent. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1605477113 (2016)



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