BACTERIAL SECRETION

The two faces of MycP1

Mycobacterium tuberculosis uses ESX1, a type VII secretion system, to deliver virulence factors into host cells. Because some of the proteins secreted by ESX1, such as ESAT6 (also known as EsxA), are important for virulence and also highly immunogenic, the system is transcriptionally regulated to maintain a balance between virulence and immunogenicity. Ohol *et al.* now reveal that ESX1 is further regulated by the subtilisin-like serine protease MycP1, which is part of the ESX1 complex.

Clues that MycP1 might regulate ESX1 came from the observation that ESX1-secreted protein B (EspB) is cleaved by an unknown protease at its carboxyl terminus following secretion — the C terminus of EspB is required for interaction with and, consequently, secretion of ESAT6. Indeed, the authors showed that EspB is processed by MycP1 *in vitro*. Furthermore, loss of MycP1 abolished ESX1-mediated secretion *in vitro*, confirming that MycP1 has an integral role in this process. Interestingly, however, MycP1-mutant bacteria reconstituted with protease-inactive MycP1 showed increased ESX1-mediated secretion. Therefore, MycP1 has a dual role: although it is required for ESX1-mediated secretion, its protease activity inhibits this process.

Because ESX1-mediated secretion is important for virulence, the authors sought to investigate the effect of the loss of MycP1 or MycP1 protease activity in macrophage infection. As expected, bacteria lacking MycP1 did not elicit a strong immune response (for example, increased interferon- β mRNA levels). However, bacteria with protease-inactive MycP1 triggered a more robust

immune response than wild-type bacteria, which suggests that the loss of MycP1 protease activity induces enhanced innate immune responses by increasing ESX1-mediated secretion, in particular of immunogenic proteins such as ESAT6. These findings were also confirmed *in vivo*: mice infected with MycP1-mutant bacteria and bacteria carrying protease-inactive MycP1 showed higher survival rates than those infected with wild-type bacteria.

On the basis of their findings, the authors propose that MycP1 might be necessary for ESX1-mediated secretion because it is required for complex formation. However, MycP1 inhibits further ESX1-mediated secretion by cleaving full-length EspB (the protein that promotes the secretion of other substrates, such as ESAT6), thereby avoiding immune detection and ensuring bacterial survival.

Rachel David

ORIGINAL RESEARCH PAPER Ohol, Y. M. *et al.* *Mycobacterium tuberculosis* MycP1 protease plays a dual role in regulation of ESX-1 secretion and virulence. *Cell Host Microbe* 7, 210–220 (2010)

FURTHER READING Abdallah, A. M. *et al.* Type VII secretion — mycobacteria show the way. *Nature Rev. Microbiol.* 5, 883–891 (2007)