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A possible mechanism of drug tolerance in mycobacteria

In this study, the authors investigated possible mechanisms of drug tolerance in mycobacteria and identified a key mediator to target with drug therapy, with the aim of shortening current treatment and moving towards eradication.

Using an in vivo model, they found that drug tolerant mycobacteria existed in macrophages prior to granuloma formation, indicating that the granuloma is not essential for developing tolerance, but is important for dissemination. By monitoring the movement of individual macrophages from a particular granuloma they observed that these macrophages could leave the granuloma and recruit other macrophages to create new granulomas, often at sites distant from the original. This explained a well-established phenomenon in human tuberculosis infection.

The group confirmed the importance of macrophages in the induction of drug tolerance and showed that efflux pumps are essential for both bacterial growth and development of drug tolerance. They found that bacteria retained intracellularly induced tolerance when they became extracellular. This explained how tolerant extracellular bacteria could arise in the granuloma's necrotic core in human tuberculosis infection.

By challenging current dogma, the researchers have established the important role of macrophages and granulomas in inducing and disseminating tolerance. They have found efflux pumps to be a useful specific target of drug therapy due to their role in tolerance and bacterial growth.

► **Adams KN**, Takaki K, Connolly LE, *et al*. Drug tolerance in replicating mycobacteria mediated by a macrophage-induced efflux mechanism. *Cell* 2011;**145**:39—53.

S V Ranson

Correspondence to S V Ranson, St Mary's Hospital, London, UK; svranson@googlemail.com

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