New TB treatments hiding in plain sight

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As tuberculosis (TB) toll is revised upward according to the WHO’s last estimates, the lack of vaccine strategy and the lengthy antibiotic treatments that unfortunately promote the emergence of drug resistance are a major set back in the fight against this pathogen. In this issue of EMBO Molecular Medicine, Schiebler et al (2015) propose a novel and compelling new approach to target Mycobacterium tuberculosis (Mtb) by pharmacologically stimulating intracellular mycobacteria clearance through autophagy.

CBZ is a sodium channel inhibitor that is commonly used to treat epilepsy and neuropathic pain. How many degrees of separation lie between these neurological effects and those that limit the replication of Mtb? When the authors examined the mechanism underlying CBZ activity, they uncovered a series of surprising connections. They found that in phagocytes, CBZ inhibits the sodium-dependent inositol transporter SCNSA. Blockade of this transporter decreased the intracellular pools of inositol leading to a concomitant decrease in PIP2 and IP3 that reduces mitochondrial Ca2+ and ATP levels. The drop in intracellular ATP subsequently activates AMP kinase (AMPK) and ULK1 to drive autophagy activation and mycobacterial killing (Fig 1). This pathway is distinct from autophagy that is triggered by the classical activator, rapamycin, as CBZ treatment does not alter S6 and p70S6 kinase phosphorylation and is independent of mTOR.

These elegant cell biological studies will serve as a starting point to understand the effects of CBZ in vivo. While the selective autophagy observed in cultured macrophages can serve a direct antimicrobial role, the effects of this ubiquitous process on the immune response are more complex. For example, much of the same cellular machinery that is involved in the clearance of intracellular bacteria also limits inflammation by disposing of damaged mitochondria (Choi et al, 2013). This functional overlap makes it difficult to ascribe the protective effects of autophagy in vivo to a simple antimicrobial activity. Indeed, previous studies suggest that regulation of the inflammatory response by autophagy may play a dominant role in protecting an intact animal from Mtb infection (Castillo et al, 2012). Similarly, Schiebler and colleagues find that treatment of infected macrophages with CBZ both increases Mtb killing and alters cytokine

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secretion (Schiebler et al., 2015). Understanding how long-term CBZ treatment influences immunopathology and tissue repair mechanisms is an important next step in understanding the benefit of this treatment.

Ultimately, any new treatment for TB would be used in the real world where genetic variation in host and pathogen, co-infections, and metabolic disorders all influence the expression of TB disease and could similarly influence the efficacy of a host-directed therapy. This is particularly relevant for CBZ, as several of these predisposing factors could directly influence autophagy. For example, the gene encoding the critical ubiquitin ligase, PARKIN, is functionally polymorphic in humans (Manzanillo et al., 2013). Similarly, the induction of STING-dependent autophagy relies on activity of the specialized type VII secretion system of the bacterium, which varies in different clinical isolates of Mtbc (Watson et al., 2012). Finally, and perhaps most significantly, metabolic disorders such as diabetes mellitus are becoming the most significant risk factor for TB worldwide and are known to alter the same AMPK-dependent pathways that are ultimately impacted by CBZ (Martinez & Kornfeld, 2014). Thus, it seems likely that this type of host-directed therapy will be most useful when targeted to a specific population.

The critical interplay between metabolic and antimicrobial pathways in the phagocyte is highlighted by a second recent article, which describes the repurposing of another commonly used drug as an autophagy-inducing TB therapy (Singhal et al., 2014). Like CBZ, the anti-diabetic, metformin (MET), has the ability to induce autophagy in an mTOR-independent manner by activating AMPK (Fig 1). Singhal et al report that this compound also shares the ability to restrict Mtbc growth in both macrophages and mice. Importantly, metformin-containing regimens improve TB outcome in diabetic patients, validating AMPK activators such as MET and CBZ as candidate adjunctive TB therapies, particularly in the context of diabetes.

The remarkable protective effect of CBZ and MET during Mtbc infection was unanticipated. However, given the central role of autophagy in both maintaining phagocyte physiology and promoting antimicrobial activity, the functional connections between metabolism and immunity that are described in these studies should not have been surprising. Indeed, as the intricate connections between metabolism, cell biology, and immunity become more apparent, the distinctions between antibiotics and modulators of host cell function may become less relevant.

References

Bradfute SB, Castillo EF, Arko-Mensah J, Chauhan S, Jiang S, Mandell M, Deretic V (2013) Autophagy as an immune effector against tuberculosis. Curr Opin Microbiol 16: 355–365

Casenghi M, Cole ST, Nathan CF (2007) New approaches to filling the gap in tuberculosis drug discovery. PloS Med 4: e293

Castillo EF, Dekonenko A, Arko-Mensah J, Mandell MA, Dupont N, Jiang S, Delgado-Vargas M, Timmins CS, Bhattacharya D, Yang H et al (2012) Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation. Proc Natl Acad Sci USA 109: E3168–E3176

Choi AM, Ryter SW, Levine B (2013) Autophagy in human health and disease. New Engl J Med 368: 651–662

Manzanillo PS, Ayres JS, Watson RO, Collins AC, Souza G, Rae CS, Schneider DS, Nakamura K, Shiloh MU, Cox JS (2013) The ubiquitin ligase parkin mediates resistance to intracellular pathogens. Nature 501: S12–S16

Martinez N, Kornfeld H (2014) Diabetes and immunity to tuberculosis. Eur J Immunol 44: 617–626

Nunes-Alves C, Booty MG, Carpenter SM, Jayaraman P, Rothchild AC, Behar SM (2014) In search of a new paradigm for protective immunity to TB. Nat Rev Microbiol 12: 289–299

Schiebler M, Brown K, Hegyi K, Newton SM, Renna M, Hepburn L, Khapholz C, Coulter S, Obregón-Henao A, Tamayo MH et al (2015) Functional drug screening reveals anticonvulsants as enhancers of mTOR-independent autophagic killing of Mycobacterium tuberculosis through inositol depletion. EMBO Mol Med 7: 127–139

Singhal A, jie L, Kumar P, Hong GS, Leow MK, Paleja B, Tsenova L, Kurepina N, Chen J, Zolezzi F et al (2014) Metformin as adjunct antituberculosis therapy. Sci Transl Med 6: 263ra159

Watson RO, Manzanillo PS, Cox JS (2012) Extracellular M tuberculosis DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. Cell 150: 803–815

WHO (2010) WHO global tuberculosis control report 2010. Summary. Cent Eur J Public Health 18: 257

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