A new path for killing pathogenic bacteria

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Bacteria that cause tuberculosis, leprosy and other diseases, survive by switching between two different types of metabolism. EPFL scientists have now discovered that this switch is controlled by a mechanism that constantly adapts to meet the bacterium's survival needs, like a home's thermostat reacting to changes in temperature.

Mycobacteria are a category of pathogenic bacteria that causes tuberculosis, leprosy, and various infections that harm people with compromised immune systems, e.g. AIDS patients. When in the human body, mycobacteria produce energy by metabolizing fats through a "cycle" of biochemical reactions. Along the way, the cycle also produces a molecule that the bacterium can take away to use elsewhere, thus stopping the energy-producing cycle. EPFL scientists have now found that mycobacteria can switch between these two routes by using a "volume control" mechanism that improves their survival. The findings, published in *Nature Communications*, could prove critical for developing new treatments.

The molecule in question is called isocitrate, which, once produced, can go in two directions: continue the energy production cycle or be taken away to synthesize other parts of the bacterium. But if isocitrate goes the biosynthesis route, it must be replenished or else the energy-producing cycle will stop. Devastating though it sounds, this does present an excellent target for killing off an infecting mycobacterium.

The key to controlling which route isocitrate will take seems to lie in the enzymes surrounding all these reactions: the enzyme isocitrate

dehydrogenase keeps it for the fat-metabolism and energy production cycle; the enzymes isocitrate lyase and malate synthase divert it away into biosynthetic processes in the bacterium.

This motivated the lab of John McKinney at EPFL, in collaboration with the lab of Uwe Sauer at ETH Zürich, to look at how mycobacteria activate or inactivate the genes of these enzymes. The researchers used a genetic technique called "gene deletion", which involves removing a specific gene in a bacterial strain and observing the consequences. Using this method, they produced various strains of mycobacteria without the genes that code for the enzymes of interest.

The results showed that the mycobacterium decides where to direct isocitrate by using a mechanism that is not like a simple on-off switch. Instead, lead author Paul Murima (EPFL) describes it as a thermostat that controls a home's heating system in response to temperature fluctuations: "If the temperature becomes too high, a thermostat cools the house down; if it gets too low it heats it up. Similarly, the mechanism that controls how isocitrate is used responds to negative feedback, and so it dampens 'noise' to maintain optimal levels."

The mechanism is appropriately adaptable and flexible, quickly responding to the dynamic environments in which the bacterium can find itself. Interestingly, the mechanism is also different from that used by gut bacteria. This means that if it becomes a target of future treatments, it should not affect the patient's microbiome, which increasing evidence shows to be intimately linked to the healthy function of the immune system.

More information: Murima P, Zimmermann M, Chopra T, Pojer F, Fonti G, Dal Peraro M, Alonso S, Sauer U, Pethe K, McKinney JD. A rheostat mechanism governs the bifurcation of carbon flux in mycobacteria. *Nature Communications* Aug. 24, 2016. DOI:

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