# Study uncovers evidence on how drug-resistant tuberculosis cells form

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A new study led by Harvard School of Public (HSPH) researchers provides a novel explanation as to why some tuberculosis cells are inherently more difficult to treat with antibiotics. The discovery, which showed that the ways mycobacteria cells divide and grow determine their susceptibility to treatment with drugs, could lead to new avenues of drug development that better target tuberculosis cells.

The study appears December 15, 2011 in an advance online edition of *Science*.

"We have found that the consequences of the simple and unexpected patterning of mycobacterial growth and division means some bacterial cells have the capacity to survive in the face of antibiotics," said Bree Aldridge, a postdoctoral fellow at HSPH and co-first author of the study.

Tuberculosis is an infectious disease that kills more than 1.5 million people annually. It is a difficult disease to treat; people are prescribed a combination of antibiotics to be taken daily for six to nine months, a regimen that is hard for patients to follow and for nurses and doctors to administer. Even after beginning appropriate treatment, it appears that some of the infectious cells survive for long periods of time.

The HSPH researchers, led by Aldridge, co-first author and visiting scientist Marta Fernandez-Suarez, and senior author Sarah Fortune, assistant professor of immunology and infectious diseases, along with colleagues from Massachusetts General Hospital, set out to determine

what distinguishes a cell that lives from one that dies. They designed a unique microfluidic chamber in which they grew Mycobacterium smegmatis cells (which behave similarly to Mycobacterium tuberculosis cells) and filmed their growth with a live-cell imaging system.

The researchers thought that the M. smegmatis cells would divide evenly into similar-sized daughter cells, as bacteria such as E. coli do. Instead, they were surprised to find that the M. smegmatis daughter cells were incredibly diverse, with highly variable sizes and growth rates. They found that this diversity arises because M. smegmatis grow in an unusual fashion, elongating from only one end. When an asymmetric mother cell divides, it creates daughter cells that are very different from one another in fundamental ways, including their growth properties.

The researchers speculated that these physiologically distinct subpopulations of cells would translate into differences in their susceptibility to antibiotics, which target processes essential for growth and division. To test this hypothesis, they treated the cells with different classes of antibiotics and observed how subpopulations of daughter cells responded.

The results showed that the different daughter cells exhibited varying susceptibilities to the treatments, strong evidence that populations of mycobacterial cells contain cells that are inherently tolerant of antibiotics and providing an important piece to the puzzle of why tuberculosis is such a difficult disease to treat.

"It is surprising to discover that mycobacteria differ from other bacteria such as E. coli in such a fundamental way," said Fortune. "It is easy to assume that most bacteria work in a similar fashion. While that's true sometimes, this study shows that bacterial species, such as TB, may be strikingly different from each other and thus require different methods of treatment." The researchers hope that their findings lead to the

development of treatment regimens in which antibiotics are combined to specifically target tolerant subpopulations of cells.

**More information:** "Asymmetry and aging of mycobacterial cells leads to variable growth and antibiotic susceptibility," Bree B. Aldridge, Marta Fernandez-Suarez, Danielle Heller, Vijay Ambravaneswaran, Daniel Irimia, Mehmet Toner, Sarah Fortune, *Science*, online Dec. 15, 2011

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