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"Single-cell analysis of persistence in mycobacteria".

Abstract:

Tuberculosis (TB) is notoriously difficult to treat and multiple antibiotics must be administered for 6-9 months to achieve a lasting cure. Why aren't antibiotics more effective? In part, because bacteria exposed to antibiotics display biphasic survival kinetics comprising an exponential "killing phase" followed by a "refractory phase" in which the death rate slows dramatically and a subpopulation of bacteria persists. These "persister" cells are phenotypic variants within isogenic populations that somehow tolerate prolonged exposure to antibiotics. Using microfluidics and time-lapse fluorescence microscopy, we have studied persistence at single-cell resolution in fast-growing (Mycobacterium smegmatis) and slow-growing (Mycobacterium tuberculosis) mycobacteria. Our results demonstrate that there is no correlation between persistence and the growth rates of individual bacteria. These observations are in sharp contrast to the widely accepted hypothesis that persisters comprise pre-existing subpopulations of slow- or non-growing cells that are selected by antibiotic exposure. We have applied the microfluidics-microscopy approach to the frontline anti-TB drugs as well as new candidate drugs that are under development. Our results and conclusions from these experiments will be presented.