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1F Lounge, Quantitative Biology Bldg. A, Osaka

Single-cell imaging study of bacterial antibiotic tolerance

Summary
In this talk, I will present our recent works on studying bacterial antibiotic tolerance using single-cell imaging. Natural variations in gene expression provide a mechanism for multiple phenotypes to arise in an isogenic bacterial population. In particular, a sub-group termed persisters show high tolerance to antibiotics. Previously, their formation has been attributed to cell dormancy. Here we demonstrate that bacterial persisters, under β-lactam antibiotic treatment, show less cytoplasmic drug accumulation as a result of enhanced efflux activity. Consistently, a number of multi-drug efflux genes, particularly the central component TolC, show higher expression in persisters. Time-lapse imaging and mutagenesis studies further establish a positive correlation between tolC expression and bacterial persistence. The key role of efflux systems, among multiple biological pathways involved in persister formation, indicates that persisters implement a positive defense against antibiotics prior to a passive defense via dormancy. On the other hand, we also monitored the process of bacterial regrowth after surviving antibiotic attack at the single-cell level and found that each individual survival cell shows different 'dormancy depth', which in return regulates the lag time for cell resuscitation after removal of antibiotic. We established that protein aggresome - a collection of endogenous protein aggregates - is an important indicator of bacterial dormancy depth, whose formation is promoted by decreased cellular ATP level. For cells to leave the dormant state and resuscitate, clearance of protein aggresome and recovery of proteostasis are required. We revealed the ability to recruit functional DnaK-ClpB machineries, which facilitate protein disaggregation in an ATP-dependent manner, determines the lag time for bacterial regrowth.