Asymmetric Cell Division: A Persistent Issue?

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Heterogeneity within a clonal population of cells can increase survival in the face of environmental stress. In a recent issue of Science, Aldridge et al. (2012) demonstrate that cell division in mycobacteria is asymmetric, producing daughter cells that differ in size, growth rate, and susceptibility to antibiotics.

More than two billion people worldwide are infected with tuberculosis, and ten percent of these individuals are expected to develop active disease during their lifetime (Russell et al., 2010). The remarkable success of Mycobacterium tuberculosis in the modern age of antibiotics can be attributed, in part, to its ability to survive prolonged treatment with chemotherapeutics. Typical treatment regimens for tuberculosis can last up to 9 months and require the use of multiple drugs. Why M. tuberculosis requires such extensive treatment is unclear, although it is possible that heterogeneity in antibiotic susceptibility—even within a clonal population of cells—may play a major role.

Heterogeneity can arise stochastically, as is probably the case in the formation of dormant cells called persisters that are highly tolerant to antibiotics (Lewis, 2010). Intriguingly, a recent study suggests that heterogeneity in mycobacteria may also result from a deterministic process, namely asymmetric cell division (Aldridge et al., 2012). With time-lapse microscopy, Aldridge et al. (2012) find that every cell division for mycobacteria produces daughter cells that grow at different rates. This asymmetry ultimately stems from the fact that mycobacterial cells preferentially grow from only one pole. Cell division thus produces one fast-growing daughter cell containing the growth pole, and another, slower-growing daughter cell that must assemble a growth pole de novo. Importantly, the authors find that these growth rate differences are associated with different antibiotic susceptibilities.

These recent findings with mycobacteria underscore the fundamental asymmetry of cell division in all rod-shaped bacteria. Their cell divisions typically occur through binary fission, producing cells with a “new” pole proximal to the division plane and an “old” pole distal to it (Figure 1A). Thus, even division events that produce apparently identical daughter cells—as in E. coli—have an underlying asymmetry. Indeed, E. coli cells with older poles tend to grow more slowly and have an increased risk of dying compared to cells with younger poles (Stewart et al., 2005). In other cases, cells exploit this asymmetry to generate functional specialization of daughter cells. For example, in the oligotrophic bacterium Caulobacter crescentus, different organelles are produced at the poles, with a tubular stalk located at the old pole and a flagellum synthesized at the new pole during each cell cycle (Curtis and Brun, 2010); every cell division for C. crescentus thus yields dimorphic daughter cells (Figure 1B).

Aldridge et al. (2012) find that mycobacteria also leverage this asymmetry between the old and new pole to generate diversity among daughter cells. With time-lapse imaging of M. smegmatis, a non-pathogenic relative of M. tuberculosis, the authors observe that individual cells are highly variable in elongation rate and in the symmetry of cell sizes after division compared to E. coli. To determine whether this variability arises from differences in the growth rate of daughter cells, the authors pulse-label the cell wall with a fluorescent amine-reactive dye and then track the growth of the unlabeled poles. Surprisingly, they find that new growth occurs almost exclusively from the old pole. This contrasts with rod-shaped bacteria like E. coli that grow mainly through the insertion of new cell wall material throughout the cell body (de Pedro et al., 1997). The localization of growth at the old pole in mycobacteria creates two classes of cells after division: “accelerators” that inherit the old pole and continue growing and “alternators” that must fashion a new growth pole before elongating (Figure 1C). The mechanistic basis for this growth asymmetry is unclear, but could involve the protein DivIVA/Wag31. In Streptomyces coelicolor, DivIVA marks sites for apical growth and is sufficient to direct growth at ectopic sites when overproduced (Hempel et al., 2008). The mycobacterial homolog Wag31 was previously found to strongly localize to the old pole and to exhibit a delay before localization to the new pole (Kang et al., 2008).

Further single-cell measurements from Aldridge et al. (2012) reveal that accelerator cells tend to elongate faster than alternator cells, as expected if alternators must generate a new growth pole after each division. Accelerators are also born at a larger size, suggesting that unipolar growth continues even after formation of the division septum. Interestingly, the authors observe that the age of the accelerator cell, and hence the age of the growth pole, also has an effect on growth rate and size after division. Accelerators that have gone through two division events elongate faster and are born at a larger size than accelerators who have gone through only one division event. This trend holds up only to a certain point—in some microcolonies, accelerators appear to “reset” their growth rate and grow more slowly than their sister cells with younger growth poles.

The net result of this unusual unipolar growth is a population of cells that is clearly heterogeneous in cell size and growth rate. But is there a functional purpose to such heterogeneity? One possibility is that the slower growth rate of...
alternator cells renders them more resistant to antibiotics, particularly those targeting processes that occur only in growing cells, such as cell wall synthesis. Consistent with this notion, the authors demonstrate that alternator cells are more resistant to the cell wall synthesis inhibitors meropenem and cycloserine. However, alternator cells are more sensitive to the transcriptional inhibitor rifampicin, suggesting that there may be additional physiological differences between alternators and accelerators that are not yet clear.

The generation of heterogeneity that results from unipolar growth may constitute a type of bet-hedging strategy against antibiotics or other environmental stresses (Veening et al., 2008). More work is clearly needed to elucidate how unipolar growth occurs, how it is regulated both temporally and spatially, and what all of its functional consequences are. The work of Aldridge et al. (2012) with mycobacteria indicates that such studies could have major consequences for understanding tuberculosis and bacterial pathogenesis.

REFERENCES


Neutrophils under Tension

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An article by Houk et al. (2012) in Cell provides insight into the mechanisms confining membrane protrusions to the front of migrating neutrophils. The authors rule out a role for diffusion of inhibitory signals and show that membrane tension is necessary and sufficient to restrict signals that lead to protrusions.

Neutrophils readily polarize in response to chemoattractants and migrate through coordinated protrusions at their leading edge and retractions at their back. Efficient and persistent neutrophil migration requires the maintenance of cell polarization. When cells migrate up a chemoattractant gradient, polarization maintenance can be envisioned as the continuous response to an anisotropic environment. However, when neutrophils migrate in an isoform, isotropic environment, maintained polarization suggests that a semiautonomous excitable network is activated (Iglesias and Devreotes, 2011).

Positive and negative feedback loops have been implicated in maintaining...