MICROBIOLOGY

Cannibals Defy Starvation and Avoid Sporulation

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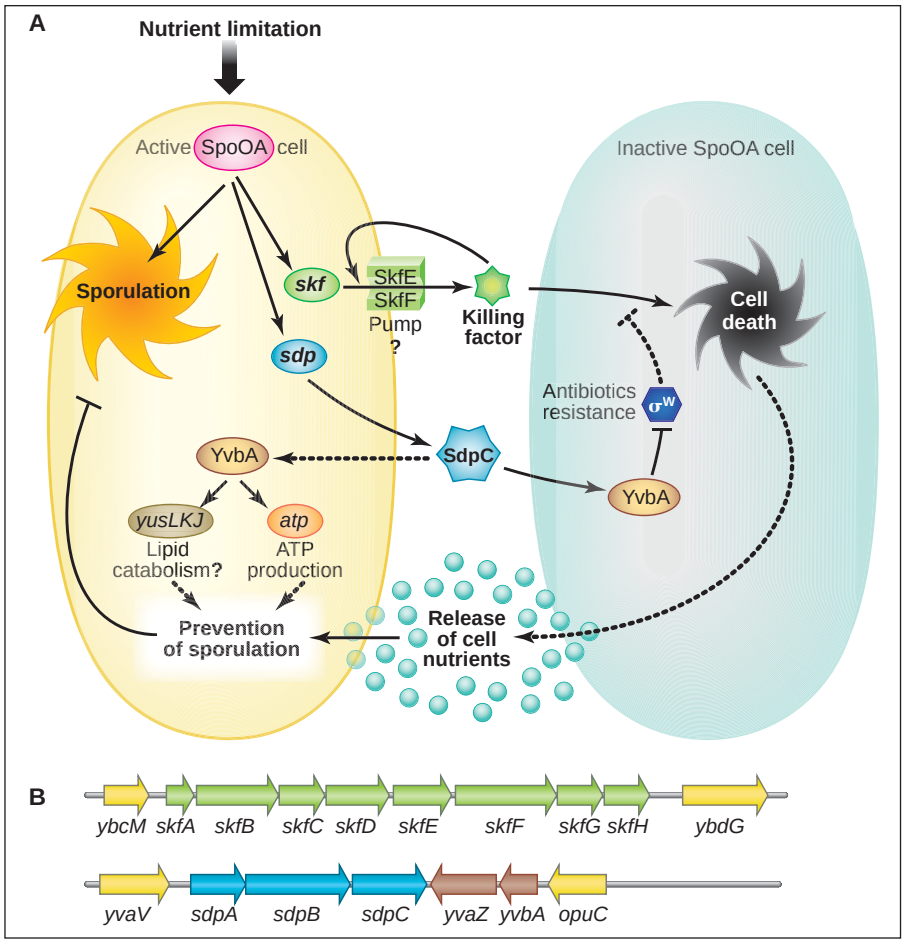
The term "programmed cell death" (PCD) refers to any form of cell death mediated by an intracellular death program. Although PCD is generally associated with multicellular eukaryotic organisms, PCD has also been found in prokaryotes (*1*–*3*). Well-characterized PCD systems in bacteria include the "toxin-antitoxin" modules located on extrachromosomal elements (such as plasmids or phages) (*2, 3*) and homologous modules located on the bacterial chromosome that are activated by a decrease in nutrients (*3, 4*). Under starvation conditions, it may be advantageous for a fraction of a bacterial population to undergo PCD, thus providing nutrients for the remaining cells (*1, 3*). On page 510 of this issue, González-Pastor, Hobbs, and Losick describe a new PCD system in the bacterium *Bacillus subtilis* (*5*) that is crucial for spore formation (sporulation) (*6, 7*). In a process that the authors term "cannibalism," some cells resist sporulation by killing other sister cells, enabling them to feed on the released nutrients.

Nutrient limitation triggers spore formation, and entry into this process is governed by the regulatory protein SpoOA (*8*). In earlier work, Losick and co-workers discovered that SpoOA regulates two additional operons: *skf* (sporulating killing factor) and *sdp* (sporulating delay protein) (see the figure), which are strongly induced at the beginning of sporulation (*9*). Now, González-Pastor *et al*. (*5*) show that the *skf* operon is involved in the production of an extracellular killing factor during sporulation. The operon, through its products SkfE and SkfF, also confers resistance to the killing factor. SkfE resembles an adenosine triphosphate (ATP)–binding cassette, and SkfF resembles a transport complex (ABC transporter). It is possible that together these two factors form an export pump that pumps the killing factor out of the cells.

The second operon controlled by SpoOA is *sdp* (see the figure). SdpC is responsible for producing a 5-kilodalton extracellular factor that acts as a signaling protein among bacteria. SdpC strongly controls the transcription of a two-gene operon, *yvbA* and *yvaZ*, located immediately downstream of the *sdp* operon. Artificially inducing *yvbA* is sufficient to delay sporulation. A search for genes that could be under the control of the YvbA transcription factor turned up the ATP synthetase operon, which is responsible for ATP production, and the *yusLKJ* operon, whose inferred products are similar to lipid catabolism enzymes. High levels of expression of *yusLKJ* were dependent on both the signaling protein SdpC and YvbA. Thus, the signaling protein switches on synthesis of YvbA, which in turn causes an



Defying starvation. When faced with a decrease in nutrients, a subpopulation of a *B. subtilis* culture delays sporulation (**A**) by activating the regulatory protein SpoOA, which switches on a series of operons (**B**). In SpoOA-active cells, SpoOA delays sporulation by switching on two operons, *skf* and *sdp*. The *skf* operon is involved in the production of an extracellular killing factor. Its other two products, SkfE and SkfF, antagonize the lethal action of the killing factor, probably by forming an export pump that pumps the factor out of the SpoOA-active cells. In contrast, cells containing inactive SpoOA are killed by the secreted killing factor, resulting in the release of nutrients that can be consumed by SpoOA-active cells. In this way, SpoOA-active cells can postpone sporulation. In both active and inactive SpoOA cells, a gene product of the *sdp* operon (SdpC) switches on expression of the transcription factor YvbA. This factor seems to delay sporulation in SpoOA-active cells, probably by activating lipid catabolism and ATP-producing enzymes. In contrast, in SpoOA-inactive cells, YvbA contributes to *skf*-dependent cell death, probably by inhibiting sigma factor σ^W, which is responsible for detoxification and antibiotic resistance. Question marks and dashed lines represent sections of this model that are yet to be confirmed.

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increase in energy production. Because a depletion of energy resources triggers sporulation, this increase in energy production could be responsible for delaying the onset of sporulation.

On the basis of their results, González-Pastor and colleagues have proposed an intriguing model in which a new PCD pathway enables a subpopulation of *B. subtilis* to delay entry into sporulation. Upon nutrient limitation, the key regulatory protein SpoOA is activated, but only in a subpopulation of cells (SpoOA-active); the rest of the cells remain SpoOA-inactive. When death through starvation is imminent for the whole population, a regulatory cascade is induced in the SpoOA-active cells. First, the *skf* operon is switched on and, as a consequence, the cells produce the killing factor and the pump (SkfE and SkfF). The pump exports the killing factor out of the cells, thereby protecting them from PCD. In contrast, SpoOA-inactive cells produce neither the killing factor nor the pump, and thus are lysed by the killing factor pumped out of the SpoOA-active cells. In the SpoOA-active cells, the *sdp* operon is also switched on, leading to the production of the signaling protein (SdpC) and hence to the transcription of the *yvbA* gene. YvbA turns on the operons for ATP synthetase (*atp*) and for lipid catabolism enzymes (*yusLKJ*), thus delaying entry of the SpoOA-active cells into the sporulation program. However, *YvbA* is also induced by the SdpC signaling protein in SpoOA-inactive cells. González-Pastor and colleagues suggest that YvbA contributes to the death of SpoOA-inactive cells by repressing the gene for sigma factor (σ^W). Sigma factor may protect cells from being lysed by the killing factor because it is involved in resistance to antibiotics and in detoxification. Thus, in SpoOA-inactive cells, YvbA acts cooperatively with the killing factor to cause cell lysis. As a result, nutrients are released, providing food for SpoOA-active cells, which enables them to keep growing rather than entering sporulation.

How could this PCD pathway benefit bacterial populations? Sporulation is an energy-intensive process that is irreversible after the early stages. If food resources become available during later stages, sporulating cells would be at a disadvantage relative to bacteria that could initiate growth immediately. For the bacterial population as a whole, it is beneficial to delay the onset of sporulation.

The new study tests the PCD response in *B. subtilis* both genetically and physiologically. The data raise some compelling questions that may be answered by future molecular and population studies: How does *skf* induce cell death? Is the killing factor actually a product of the *skf* operon, or does *skf* merely regulate this factor? Is the killing factor specific for *B. subtilis* or is it a more general antibiotic? Do SkfE and SkfF actually form a pump? And finally, is there a genetic program that decides whether a given cell will become SpoOA-active or stay SpoOA-inactive, or does this happen randomly?

The new work is important not only because it increases our understanding of *B. subtilis* sporulation, but also because it supports a new way of looking at bacterial cultures as multicellular organisms (*10, 11*). PCD, together with differentiation and intercellular communication, are indicators of the multicellularity of bacterial cultures (*3*). It seems that both chromosomal toxin-antitoxin PCD systems (*3*) and the killing response of *B. subtilis* during sporulation (*5*) are examples of multicellular behavior in bacterial cultures under conditions of severe nutrient limitation. González-Pastor and colleagues term the killing that takes place during sporulation as "cannibalism." We would prefer to call it "self-digestion." Rather than the notion of some bacteria "cannibalizing" others, the term "self-digestion" suggests that the bacterial culture acts like a multicellular organism that, when challenged by starvation, digests parts of itself to keep the whole alive.

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ECOLOGY

Global Climate Change Strikes a Tropical Lake

Daniel A. Livingstone

Global circulation models predict that global warming caused by greenhouse gases will be particularly marked at high latitudes. Possibly so, but lower latitudes do not escape unscathed. On page 505 of this issue, Verburg *et al.* (*1*) demonstrate a profound effect of global warming on Lake Tanganyika, just south of the equator in tropical Africa.

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Lake Tanganyika is one of the oldest and deepest lakes in the world. Its great mass of water gains and loses so little through rivers that its water renewal time is measured in millennia rather than years or decades. One might expect the great thermal inertia of so much water to buffer the lake against the vagaries of climate change. The work of Verburg *et al.* contradicts that expectation.

Many animal species that live nowhere else are endemic to Lake Tanganyika. There are hundreds of endemic species of fish, not all of which are in the notoriously fast-evolving cichlid family, and scores of endemic molluscs and ostracod crustaceans (see the figure). Even many genera are restricted to this single lake. Among the endemic species are bizarre specialists, such as a caddis fly larva that gyrates on the surface like a whirligig beetle, and a mastacembelid eel that swims on its side like a flatfish (*2–4*).

The lake contains two genera of small herrings, and many of its gastropod molluscs have spiny shells like those found on tropical seashores. This led early zoologists to postulate a previous connection to the sea, but such a possibility was disproved by geological mapping between the lake and the ocean. The spectacular fauna evolved to meet the challenge of a large and stormy lake during the millions of years since its formation.

Because of its great depth, Lake Tanganyika is perennially stratified. Dead organic matter sinks from the illuminated surface zone and decays as it falls, releasing nutrient materials such as silica and phosphorus. Organisms near the surface are chronically short of these nutrients, which they need for photosynthesis; in the depths, nutrients are plentiful but there is