NEWS & VIEWS

EVOLUTIONARY BIOLOGY

Microbes exploit groundhog day

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Can microorganisms learn from history? When a sequence of environmental changes is repeated, natural selection might select for responses that enable the microbes to prepare for later challenges in the sequence.

Ivan Pavlov is famous for demonstrating that dogs can learn to associate events that occur close together in time[1]. By repeatedly preceding food delivery with an unrelated stimulus (sometimes bells, sometimes electric shocks), Pavlov was able to condition dogs to link these events. After a while, the stimulus was sufficient for the dogs to anticipate food. On page 220 of this issue, Mitchell *et al.*[2] present evidence that microorganisms can benefit from conditioned responses that allow them to prepare for environmental changes.

The proposal that microorganisms can associate a stimulus with an appropriate response to a future environment might seem far-fetched. After all, without cognition, microorganisms rely on simple regulatory networks to sense and respond to their environment. A canonical example of gene regulation, the response of *Escherichia coli* to the sugar lactose, illustrates why it seems surprising that such networks can be used to anticipate environmental changes. This bacterium activates genes needed for lactose use (the response) only in the presence of lactose or similar chemicals (the stimulus). The response is mediated by a specific interaction between lactose and a regulatory protein that lessens the activity of the protein, reducing its ability to repress the lactose genes. This direct link between the stimulus and the response makes sense: it reduces costly gene activation in the absence of lactose, while ensuring that activation occurs when it is useful.

Insight

If regulatory networks function to sense the current environment, how is it possible for them to induce a response that will be beneficial only in a future environment? The insight of Mitchell *et al.*[2], building on previous work[3], was to realize that the connection between stimulus and response can be offset in time. For example, if a non-lactose sugar consistently follows the availability of lactose, selection might favour the evolution of a regulatory network that directly links the presence of lactose to the expression of the non-lactose-utilization genes. This network would serve to 'prime' cells, conferring an advantage by preparing them to use the non-lactose sugar in anticipation of its imminent availability, and thereby reducing the lag time characteristic of *de novo* activation of response genes. Mitchell *et al.* call this mechanism adaptive anticipatory conditioning.

But how can this idea be addressed experimentally? Mitchell *et al.* examine the responses of *E. coli* and baker's yeast, *Saccharomyces cerevisiae*, to sequences of environmental changes that it is reasonable to think they may have been repeatedly exposed to throughout their evolutionary histories. For *E. coli*, the authors consider stimuli and appropriate responses associated with passage through the initial region of the gastrointestinal tract (an environment relatively high in lactose but low in the sugar maltose), and potentially adaptive responses in the lower part of the tract (an environment relatively low in lactose and high in maltose). For yeast, they consider the temporal sequence of stresses associated with fermentation: high temperature, increasing levels of ethanol and exposure to oxidative stress.

For both *E. coli* and yeast, Mitchell *et al.* find evidence that early environmental stimuli prime cells to better deal with later environments. In *E. coli*, lactose (the early stimulus) caused intermediate activation of maltose genes (the late response). This priming provided a growth benefit, relative to unprimed cells, when cells were subsequently transferred to an environment containing maltose. Similarly, in yeast, early stress stimuli induced responses that conferred protection to later stresses. For example, pre-exposure to ethanol conferred a 29-fold increase in survival to subsequent exposure to an oxidative stress that simulated late-fermentation conditions.

Priming alone, however, is not sufficient to infer that an anticipatory response has taken place. For example, it is possible that activation of maltose genes may provide *E. coli* with a benefit during growth in lactose. If so, benefits of priming following transfer to a subsequent environment could be a side effect of this direct advantage. To address this possibility, Mitchell *et al.* took advantage of an experiment in which *E. coli* were evolved in an environment containing only lactose[4]. In this environment, the temporal link between the presence of lactose and future maltose availability is removed. Consistent with the priming response being selected to prepare cells for future availability of maltose, the presence of lactose no longer induced maltose genes in the evolved strains. Moreover, this change was associated with the loss of the lactose pre-exposure advantage before transfer to maltose.

Responses

Mitchell and colleagues' experiments[2] show that microorganisms can interpret their environment and respond in a way that provides a benefit only following a future environmental change. The ecological forces, if any, selecting for this ability are less clear. Responses that seem anticipatory in carefully defined lab environments may simply be side effects of imperfect regulation, providing no benefit in complex natural environments. Alternatively, the responses could provide a direct benefit in an unknown but important environment relevant to selection in nature. Collection of detailed fitness and ecological data will be required to address these points. What are the relative costs and benefits of being primed in natural environments? How reliably does a potential stimulus precede a particular environmental change? Depending on the answers to these questions, it may turn out that other response strategies are more successful.

One message is clear. The regulatory networks that link environmental stimuli to microbial responses are complex and can evolve rapidly. The potential for microorganisms to offset responses from environments in which those responses are useful provides both a warning and an opportunity for researchers involved in testing the functional significance of links between stimuli and responses. ■

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1. Pavlov, I. P. *Conditioned Reflexes* (Dover, 1960).
2. Mitchell, A. *et al. Nature* **460,** 220–224 (2009).
3. Tagkopoulos, I., Liu, Y.-C. & Tavazoie, S. *Science* **320,** 1313–1317 (2008).
4. Oxman, E., Alon, U. & Dekel, E. *Evolution* **62,** 1547–1554 (2008).