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Environmental responses and phage susceptibility in foodborne pathogens: implications for improving applications in food safety

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Bacterial foodborne pathogens can rapidly respond to changes in their environment, granting them the ability to survive under a broad range of conditions. In doing so, they undergo physiological alterations that can influence the efficacy of detection and interventions used in the food industry. As bacteriophage-based applications in food safety are gaining traction, it is crucial that we consider the effect the environment can have on phage–host interactions. This review aims to bridge knowledge of the responses of bacterial foodborne pathogens to changing environmental conditions with our understanding of phage–host interactions. An improved understanding of these intersections will aid in the development of bacteriophage-based products for the detection, biocontrol and biosanitation of foodborne pathogens.

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Introduction

Bacterial foodborne pathogens can survive and replicate under a broad range of environmental conditions. To adapt to a changing environment they must first sense and then respond to the change; the response typically affects gene expression and leads to changes in cell physiology that favor growth or survival under the new conditions. These changes in physiological state can affect the cell's susceptibility to antimicrobials or sanitizing agents, and can interfere with detection systems. As bacteriophage-based control and sanitization products are now on the market for use in the food industry, and with phage-based detection products in development, it is necessary to consider the effect environmental conditions can have on phage–host interactions to maximize the efficacy of these new tools.

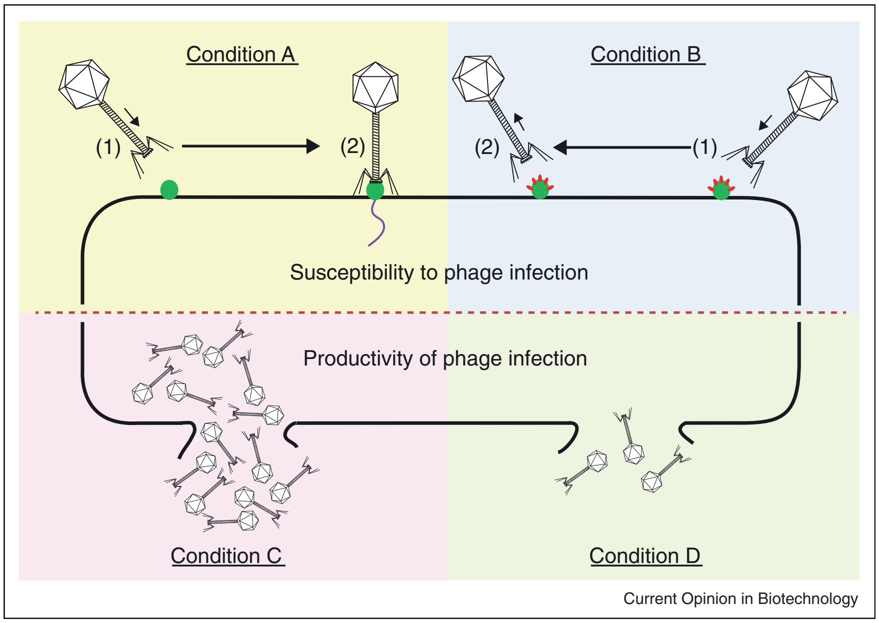
Bacteriophages are the viruses of bacteria. They are found in nearly every environment on Earth and are estimated to globally outnumber prokaryotes by ten to one [1,2]. Shortly after their co-discovery by Frederick Twort and Felix d'Herelle in the early 20th century, they were harnessed for their therapeutic potential. However, after the discovery of broad-spectrum antibiotics, phage applications were soon largely forgotten in the U.S. and in Western Europe until interest was renewed by the rise of antibiotic resistant pathogens. The development of phage-based products is now moving rapidly in the food safety sector. In 2006, a *Listeria* phage biocontrol product was approved by the USFDA for use in ready-to-eat food products [3]. The product consists of a 'cocktail' of lytic bacteriophages that can be applied directly to food to reduce or prevent contamination by *Listeria monocytogenes*. Several other phage-based control applications are also used by the food industry, and a number of new bacteriophage-based products, including detection systems, are under development. There are several current review articles that cover phage-based applications in the food industry [4] with emphasis on biocontrol [5,6,7•] and detection applications [8].

In this review we focus on how phage–host interactions are affected by environmental responses that alter the physiological state of bacterial foodborne pathogens. Host physiology can affect phage–host interactions through changing (i) the host cell's susceptibility to phage infection and/or (ii) the productivity of a phage infection (Figure 1). We define 'susceptibility' as the likelihood of a cell being lysed or lysogenized after collision with a phage, and 'productivity' as a measure of phage produced per infection over the time until lysis. It has long been established that host cell physiology affects the productivity of phage infection [9]; however, it is not clear to what extent changes in environmental conditions modulate host cell susceptibility to phage infection.

Bacteria rapidly respond to their environment

Bacterial foodborne pathogens not only have to survive in a food matrix, but most must also survive in the human host where they may then establish an infection. To do this, the cell utilizes mechanisms of signal transduction to sense changes in the extracellular environment and initiate a cellular response; such mechanisms include (i) one-component systems, which are a single protein fusion of an environment-sensing input domain and a cell-response-initiating output domain [10], (ii) two-component systems, which have input and output domains that are encoded by separate genes, (iii) extracytoplasmic functioning (ECF) sigma factors, which resemble

Figure 1



Susceptibility to phage infection and/or productivity of phage infection can be affected by environmental conditions. The dotted red line separates a hypothetical host cell that is conditionally susceptible to phage infection (with higher susceptibility under condition A as compared to condition B) from an infected cell that produces more or less progeny phage under different conditions (with the cell supporting production of more progeny under condition C as compared to condition D). Green ovals represent phage receptors, and red ovals represent structural modifications.

two-component systems, except that stimulation of the input protein leads to uncoupling and activation of a sigma factor [11], and (iv) the more complex chemotaxis systems which enable bacteria to move across a chemical gradient [12]. Bacterial cells can also respond to some environmental changes through internal sensing mechanisms such as thiol-based redox switches and temperature-dependent mRNA structures, both of which can affect gene expression [13,14]. Changes in the environment that require the rapid induction of large sets of genes often lead to a cellular response involving activation of alternative sigma factors. Once activated, alternative sigma factors can associate with RNA polymerase and redirect transcription to sets of genes that share a common promoter sequence [15]. After altering global gene expression, the cellular response ultimately leads to physiological changes that enhance the cell's growth or survival under the new conditions.

Environmental conditions impact control strategies and detection of foodborne pathogens

Environmental conditions, and their effect on cell physiology, can impact the efficacy of bacterial foodborne pathogen detection and control strategies. Detection assays that involve reactions with the surface of the pathogen, for example, antibody-based systems, have been shown to vary in efficacy when *L. monocytogenes*, *Salmonella enterica*, and *Escherichia coli* are exposed to different conditions [16]. For example, *E. coli* pre-exposed to low (3.5) or high (9) pH had been shown to produce a much smaller signal when detected with a bead-based immunoassay [17]. Similarly, the efficacies of some disinfectants are affected by growth conditions that influence surface charge and hydrophobicity of *L. monocytogenes* [18]. The bactericidal activities of a chlorine sanitizer and a 2% lactic acid solution were significantly reduced when treating sliced, versus unsliced, apples contaminated with *E. coli* and *Salmonella* [19•].

Environmental conditions and host state physiology can affect susceptibility to phage infection

It is well established that the structure and composition of the bacterial cell surface is in a constant state of flux [20••,21]. The first step of phage infection requires phage recognition of a specific surface receptor; however, it is not well understood how changes in host physiology may affect the cell's susceptibility to phage infection. As an example, components of wall teichoic acids (WTA) and acetyl groups in peptidoglycan are common phage receptors amongst Gram-positive organisms [22] and both composition and structure of WTA and peptidoglycan are known to be affected by a changing environment [23••]. Although the impact of this conditional regulation on the cell's susceptibility to phage remains to be defined