Classic Spotlight: the Physiological State of Competence and So Much More

Peter J. Christie
Department of Microbiology and Molecular Genetics, McGovern Medical School, Houston, Texas, USA

Over the past 100 years, the Journal of Bacteriology (JB) has steadfastly published reports exploring basic physiological and metabolic processes in unicellular organisms and how these processes influence microbial interactions with each other, their hosts, and the environment. The value in such studies is beautifully illustrated by tracing the history of JB publications devoted to understanding the physiological state of “competence” in bacteria. Following the initial reports by Griffith in 1928 (1) and Avery, MacLeod, and McCarthy in 1944 (2) on the transformability of pneumococci by the “transforming principle” of DNA, investigators began studying a striking phenomenon designated as the “competent or transformable physiological state.” This state refers to a short period at a specific cell density during logarithmic growth in which nearly all pneumococcal cells are able to undergo genetic transformation.

In a landmark study published in JB in 1966 (3), Alexander Tomasz presented results of a rigorous set of experiments exploring physiological parameters required for activation of competence in pneumococci. Among the parameters relating to cell growth, he described the influence of inoculum size, the phase and rate of growth, and effects of temperature, pH, and medium composition to competence development. He also defined the role of an extracellular proteinaceous factor he termed “activator” substance (4) in catalyzing the synchronous development of the transformable state through cell-to-cell propagation. Fourteen figures later, Tomasz presented his model for the regulation of the competent state in pneumococcus. Strikingly, the model is a blueprint for what we now term as quorum signaling, replete with depictions of (i) an initiation phase (noncompetent cells producing low levels of “activator”), (ii) a cell-density-dependent activation phase (noncompetent cells bearing an activator-binding site sense the activator, become competent, and release more activator, resulting in a proliferative response of transformability), and (iii) a shutdown or inhibition phase (to block energetically expensive and potentially damaging unchecked transformation). Tomasz considered this “hormone-like regulation” to be an important mechanism for synchronizing physiological states at the level of an entire cell population, thus laying a foundation for the next 50 years of studies exploring the many facets of hormone-like, quorum-based communication in bacteria (3).

By the mid-1990s, studies had shown that a 17-residue peptide, the competence-stimulating peptide (CSP), is the “activator” substance and that CSP is released from cells and activates competence development through a positive-feedback loop involving products of the comAB and comCDE operons. Critically missing, however, was the link between this peptide synthesis/sensing system and expression of genes for the DNA uptake machinery. In another stellar paper published in JB in 1999 (5), Myeong Lee and Donald Morrison solved this quandary through identification of a putative alternative sigma factor designated ComX. These investigators identified ComX through biochemical analyses of RNA polymerase preparations from competent cells and gene knockouts, the latter complicated by the fact that the pneumococcal strain under study carried two copies of comX genes. The ComX factors did not regulate the competence-sensing operons but rather regulated a set of other competence operons, each bearing a conserved cin-box motif in their upstream promoters. The Lee and Morrison model for competence regulation and development fleshes out Tomasz’s earlier model with identities of the “activator” and “activator binding site” and the peptide release/sensing circuitry, and it additionally includes their ComX link connecting this circuitry with that responsible for DNA uptake and processing. They also honed in on components responsible for an “inhibitor” that Tomasz had proposed mediates the abrupt competence shutoff phase (3). The central player appears to be ComX, which inhibits comX gene expression either directly or indirectly via a ComX-induced factor (5).

Despite the unfolding of details concerned with competence regulation, still lacking until more recently was insight into a regulatory mechanism that would ensure that pneumococcal cells develop competence only when DNA is present in the environment. Work in the past 15 years has established that transcription of at least 180 genes is altered during competence development. Functions of most of these genes are unknown, with the striking exception of a few found to play critical roles in ensuring the presence of exogenous DNA during activation of the competent state. As highlighted in a recent JB article by Berg, Ohnstad, and Hävarstein, these genes encode wall hydrolases (e.g., CpdD, LytA, and LytF) designated “fratricins.” Through a process termed fratricide, the surface-exposed or secreted fratricins kill subpopulations of noncompetent cells, thus generating a pool of exogenous DNA precisely when the bulk cell population is in the “transformable physiological state” (6). Today, an accumulating body of evidence is establishing that the regulatory systems involved in development of the competent state in pneumococci are in fact conserved among many species of streptococci. Who could have known that what began by Tomasz as the discovery and characterization of “activator substance” (3, 4) would set in action investigations that to date have identified conserved genetic circuitries linking the physiological states of streptococci to a myriad of cellular processes including—but likely not limited to—compe-

Address correspondence to Peter J. Christie at utthmc.edu.
Copyright © 2016, American Society for Microbiology. All Rights Reserved. The views expressed in this Editorial do not necessarily reflect the views of the journal or of ASM.
tence, cell-density-dependent signaling, species-targeted killing, biofilm development, and virulence?

REFERENCES