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The Major Role of Spo0A in Genetic Competence Is To Downregulate *abrB*, an Essential Competence Gene

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We show that the major role for Spo0A in the development of genetic competence is to downregulate expression of *abrB*. AbrB is both a negative regulator and a positive regulator of competence. The negative effects are exerted at multiple points in competence regulation. A regulatory mechanism that is independent of *mecA* and *abrB* operates on *comK* expression.

Genetic competence in *Bacillus subtilis* develops in response to a complex regulatory network (6, 13, 18, 33) that culminates in synthesis of the transcription factor ComK (13, 32, 33). One gene that is involved in this network specifies the transcriptionally active protein AbrB (31), which acts positively for expression of ComK (2, 13, 33). In other forms of postexponential expression, such as sporulation, AbrB acts as a transcriptional repressor that must be downregulated during the transition from exponential phase to stationary phase (22, 26, 36). This downregulation requires activation of Spo0A by phosphorylation, resulting in repression of *abrB* transcription (4, 9, 30). Therefore, AbrB accumulates in *spo0A* mutants, and certain phenotypes that result from inactivation of *spo0A* can be suppressed by loss-of-function mutations in *abrB* (8, 22, 31, 36).

Null mutants of *spo0A* are poorly transformable (2, 28), and this effect is partially reversed by inactivation of *abrB* (2). This implies that AbrB plays both negative and positive roles in the development of competence and that its concentration must be closely adjusted for optimal expression of competence. Since a *spo0A abrB* double mutant exhibits the same reduced level of competence as an *abrB* mutant (2), we propose that the major role for Spo0A in competence is to limit the intracellular level of AbrB.

Perego et al. (25) have reported that the *spo0A9V* mutation disables Spo0A as a transcriptional activator without destroying its ability to downregulate *abrB*. If the major role of Spo0A in competence is to control *abrB*, *spo0A9V* should have no effect on transformability. In fact, a *spo0C* mutation, probably identical to *spo0A9V*, had a minimal effect on genetic competence (28). We have moved *spo0A9V* into BD630, yielding the Spo$^-$ strain BD1981. The level and time course of competence development in this strain were similar to those in the wild-type strain (data not shown), in support of the model that Spo0A acts in competence development as a negative regulator of *abrB*. This hypothesis was tested further in this study.

The strains used are listed in Table 1. The growth of competent cultures, transformation, preparation of selective media, and measurement of β-galactosidase specific activity were performed as previously described (1–3). Isopropyl-β-D-thiogalactopyranoside (IPTG; at specified concentrations) or 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-Gal; 40 μg/ml) was added as required.

Competence in a *Pspac-abrB* strain. To examine the roles of Spo0A and AbrB in competence, we placed *abrB* at the *amyE* locus under control of the IPTG-regulatable *Pspac* promoter (35) by using plasmid pDR66 (15). pDR66 contains the *lacI* gene, *cat*, pBR322 *ori*, and the *Pspac* promoter, followed by a multiple cloning site, as well as flanking segments of *amyE*. A 434-bp fragment that contained only the coding sequence of *abrB* was ligated between the *Xba*I and *Sph*I sites of pDR66. The fragment was isolated from *B. subtilis* DNA by PCR, with primers 5′-GCTCTAGAGGATTTTGTCGAATAATG and 5′-ACATGCATGCAGTGTACGATGCTTACC, in which the underlined residues constitute *Xba*I and *Sph*I sites, respectively. The ligation products were used to transform BD630 with selection for *cat*, and an AmyE$^-$ transformant was shown to contain *abrB* under *Pspac* control (see below). The *cat* marker of this construct was converted to spectinomycin resistance by transformation with DNA (21). Then the normal *abrB* gene in this strain was inactivated by introduction of Δ*abrB*::*kan* or Δ*abrB*::*cat* mutations.

When *Pspac-abrB* strains were streaked on sporulation agar, an oligosporogenic phenotype was apparent in the presence of IPTG (1 mM), but not in its absence (data not shown). Transcription of *spoVG* is repressed by AbrB (36). To test the *Pspac-abrB* construct, it was introduced into a *spoVG-lacZ* strain. As expected, growth of this strain in 1 mM IPTG resulted in nearly complete repression of β-galactosidase activity. In the absence of IPTG (data not shown), *spoVG-lacZ* expression increased sharply at the transition to stationary phase (T_0).

BD2238 [*Pspac-abrB*(*spc*) Δ*abrB*::*cat*] was grown to competence in the presence of various concentrations of IPTG, and transformability was measured (Fig. 1). Growth was unaffected by IPTG. Full expression of competence was IPTG dependent in this strain, with a maximum at 0.025 mM IPTG, confirming that AbrB plays both positive and negative roles. The unnormalized transformation frequency in the presence of 0.025 mM IPTG was no different from that obtained with the wild-type (*abrB*$^+$) strain. The culture was more transformable in the absence of IPTG than in the presence of 1 to 2 mM IPTG, principally because of the leakiness of the *Pspac* promoter. These results were confirmed with a *comG-lacZ* reporter by monitoring β-galactosidase activity (data not shown). Again, the optimum level of β-galactosidase expression was achieved at 0.025 mM IPTG.

Bypass of *spo0A* in a *Pspac-abrB* background. We tested the bypass of a *spo0A* null mutation by using the *Pspac-abrB* con-

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TABLE 1. Strains used in this study

Strain	Characters	Source or reference(s)
IS8	*trpC2 spo0A9V*	25
TT31	*ΔabrB::kan*	T. Tanaka
BD630	*hisA1 leuA8 metB5*	This study
BD1197	*hisA1 leuA8 spo0AΔ204*	2, 8
BD1865	*hisA1 leuA8 spo0AΔ204 ΔabrB::kan*	This study
BD1866	*hisA1 leuA8 metB5 ΔabrB::kan*	This study
BD1959	*hisA1 leuA8 metB5 comG-lacZ(kan)*[a]	This study
BD1981	*hisA1 leuA8 spo0A9V*	25
BD2180	*hisA1 leuA8 metB5 comK-lacZ(spc)*[a]	This study
BD2188	*hisA1 leuA8 metB5 ΔabrB::kan Pspac-abrB(cat) sinR::phl*	10
BD2189	*hisA1 leuA8 metB5 Pspac-abrB(cat) ΔdegSU::kan*	20
BD2190	*hisA1 leuA8 metB5 ΔabrB::kan Pspac-abrB(cat) srfA*(Tn*917*)	16
BD2192	*hisA1 leuA8 metB5 Pspac-abrB(cat) spoVG-lacZ(kan)*	37
BD2238	*hisA1 leuA8 metB5 ΔabrB::cat Pspac-abrB(spc)*	24
BD2239	*hisA1 metB5 ΔabrB::cat Pspac-abrB(spc) spo0A12*	This study
BD2245	*hisA1 leuA8 metB5 ΔabrB::cat comK-lacZ(spc)*[a]	This study
BD2249	*hisA1 leuA8 metB5 ΔabrB::cat Pspac-abrB(spc) ΔmecA::erm comG12-lacZ(kan)*[b]	This study
BD2261	*hisA1 leuA8 metB5 ΔabrB::cat Pspac-abrB(spc) comG12-lacZ(kan)*[b]	This study
BD2312	*hisA1 metB5 spo0A12 ΔabrB::cat Pspac-abrB(spc) comG12-lacZ(kan)*[b]	This study
BD2313	*hisA1 metB5 spo0A12 ΔabrB::cat Pspac-abrB(spc) ΔmecA::erm comG12-lacZ(kan)*[b]	This study
BD2374	*hisA1 leuA8 metB5 ΔabrB::cat comG12-lacZ(kan)*[b]	This study
BD2375	*hisA1 leuA8 metB5 ΔmecA::erm comG12-lacZ(kan)*[b]	This study
BD2376	*hisA1 leuA8 metB5 ΔabrB::cat ΔmecA::erm comG-lacZ(kan)*[a]	This study
BD2377	*hisA1 leuA8 metB5 ΔmecA::erm comK-lacZ(spc)*[a]	This study
BD2378	*hisA1 leuA8 metB5 ΔmecA::erm ΔabrB::cat comK-lacZ(spc)*[a]	This study

[a] These *comG-lacZ* (18) and *comK-lacZ* (13) constructs were translational (in-frame) fusions to *lacZ* which were integrated at the *amyE* locus. The original constructs carried *cat* cassettes, which were replaced by replacement recombination with *kan* or *spc* determinants.

[b] The *comG12-lacZ* construct (17) was a Tn*917lacZ* derivative which was integrated by Campbell-like recombination to place a transcriptional *lacZ* fusion upstream from an intact copy of *comG*.

struct. However, Spo0A represses transcription of *abrB* by binding to sites (Spo0A boxes) downstream from the *abrB* promoter (30). Since these sites are present in the *Pspac-abrB* construct, the presence or absence of Spo0A might still affect synthesis of AbrB. For unknown reasons, attempts to construct *Pspac-abrB* without the Spo0A boxes were unsuccessful. Nevertheless, complete bypass of *spo0A* by *Pspac-abrB* is shown by the fact that in the presence of 0.025 mM IPTG, the level of *comG-lacZ* expression with or without a *spo0A* null mutation

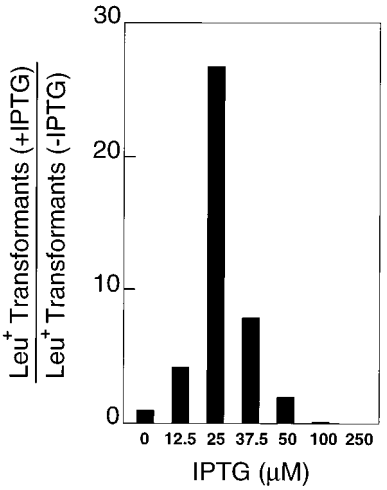

FIG. 1. Transformation of a *Pspac-abrB*(*spc*) Δ*abrB*::*cat* strain (BD2238) grown in competence medium in the presence of the indicated concentrations of IPTG. Relative transformation frequencies are expressed as ratios to the frequencies obtained with cultures grown without IPTG.

was essentially that of the *abrB*$^+$ *spo0A*$^+$ strain (Fig. 2A). However, in the *spo0A* mutant strain, the basal level of *comG-lacZ* expression was elevated compared with the basal level in the *spo0A*$^+$ strain. This difference reflects the role of the Spo0A boxes and the leakiness of *Pspac*. It is clear that the positive requirement for AbrB in competence can be fulfilled by a low (basal) level of this protein. When 2 mM IPTG was used (Fig. 2B), *comG-lacZ* expression decreased dramatically, showing that repression by excess AbrB required a relatively large amount of AbrB.

Is the only role of Spo0A in competence to control *abrB*? Although our data strongly support this conclusion, Spo0A may be involved in regulatory mechanisms which operate under other conditions or in other genetic backgrounds. Overexpression of AbrB acts at several points in the regulatory cascade. It inhibits downstream from *mecA* (27), probably by directly binding to the *comK* promoter and thus inhibiting transcription of the latter gene (17). Overexpression of AbrB (in a *spo0A* mutant) partially inhibits induction of *srfA* at T_{-1} (12, 16) and can repress transcription of *spo0H*, an essential competence gene (34, 36, 37).

The use of both positive and negative controls is typical of global regulation (29). Redundancy may ensure that only appropriate responses are triggered and may permit integration of multiple signals. The positive and negative roles of AbrB and its regulation by Spo0A may permit cells to respond to environmental conditions that are appropriate for several post-exponential responses (e.g., sporulation and competence), as well as to conditions that demand a choice among these various responses. A graded series of responses may be elicited as the concentration of AbrB in a cell decreases in response to the flow of phosphate to Spo0A. When the level of AbrB is elevated (as it is in exponential growth), both competence and

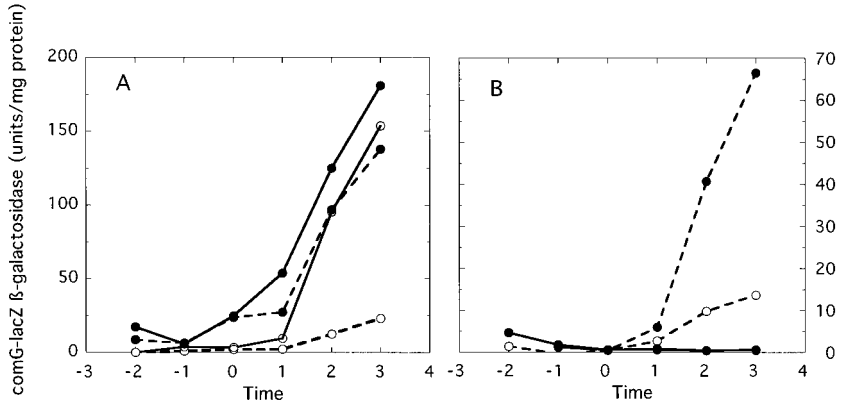

FIG. 2. Bypass of *spo0AΔ204* by growth of *Pspac-abrB* strains in the presence of 0.025 (A) and 2 (B) mM IPTG, as shown by expression of β-galactosidase from a *comG-lacZ* fusion. Dashed lines, results obtained in the absence of IPTG; solid lines, results obtained in its presence. The strains used were *Pspac-abrB*(*spc*) Δ*abrB*::*cat comG-lacZ*(*kan*) (BD2261) (○) and *Pspac-abrB*(*spc*) Δ*abrB*::*cat comG-lacZ*(*kan*) *spo0AΔ204* (BD2312) (●). Data for the *Pspac-abrB*(*spc*) Δ*abrB*::*cat comG-lacZ*(*kan*) strain in panel B are buried beneath the solid dots.

sporulation are suppressed. As AbrB decreases to an intermediate level, competence is enabled but sporulation remains inhibited. As the concentration of AbrB drops even further, sporulation begins. Thus, a common set of signal transduction molecules can determine even mutually exclusive responses.

***Pspac-abrB* does not bypass *srfA*, *degU*, or *sinR*.** *degU*, *sinR*, and a small open reading frame embedded in the *srfA* operon (5, 14) are required for expression of ComK. It is conceivable that one or more of these genes function on an unknown pathway prior to the action of AbrB. Therefore, we tested the ability of the *Pspac-abrB* construct to suppress null mutations in *degU*, *sinR*, and *srfA*. The transformabilities of appropriate mutant strains (Table 1) were monitored during growth in the presence and absence of IPTG. IPTG did not induce any increase in the level of transformation above background in any of these strains (data not shown), indicating no bypass of these inactivating mutations by AbrB synthesis.

Bypass of Spo0A deficiency and AbrB deficiency in a *Pspac-abrB* Δ*mecA*::*erm* background. Loss-of-function mutations in *mecA* exhibit two distinct phenotypes (7, 19, 23, 27). They express competence regardless of the growth medium, and they bypass the effects of null mutations in many regulatory genes, including *abrB*, on competence. Therefore, the positive effect of AbrB is exerted prior to the action of MecA. In contrast, since competence loss as a result of *spo0A* deficiency is not suppressed by *mecA* mutations, the negative effect of AbrB is exerted after or independently of MecA action. If *mecA* and *spo0A* null mutations were present in a *Pspac-abrB* background, we would expect *mecA* to bypass the positive effect of AbrB and the *Pspac-abrB* construct to permit control of *abrB*, suppressing the effect of Spo0A deficiency on competence. Indeed, in a *Pspac-abrB* Δ*mecA*::*erm spo0A*$^+$ background, *comG-lacZ* expression was similar to that of the *abrB*$^+$ strain in the absence and presence of 0.025 mM IPTG (Fig. 3A). When *spo0A* was also inactivated, *comG-lacZ* expression was not markedly affected, since the *Pspac-abrB* construct controlled accumulation of the AbrB product. In both *spo0A*$^+$ and *spo0A* backgrounds, the addition of 2 mM IPTG resulted in marked inhibition of *comG-lacZ* expression (Fig. 3B), demonstrating that the ability of AbrB to inhibit expression was unaltered.

Redundancy in *comK* regulation. MecA- and AbrB-dependent pathways converge to control the synthesis of ComK (13, 33). In the absence of MecA and with only a low basal level of AbrB, the expression of *comG-lacZ* still showed growth stage regulation (Fig. 3) (27). Thus, a third mechanism is capable of regulating *comG* expression.

To determine whether this mechanism affects *comK*, the ex-

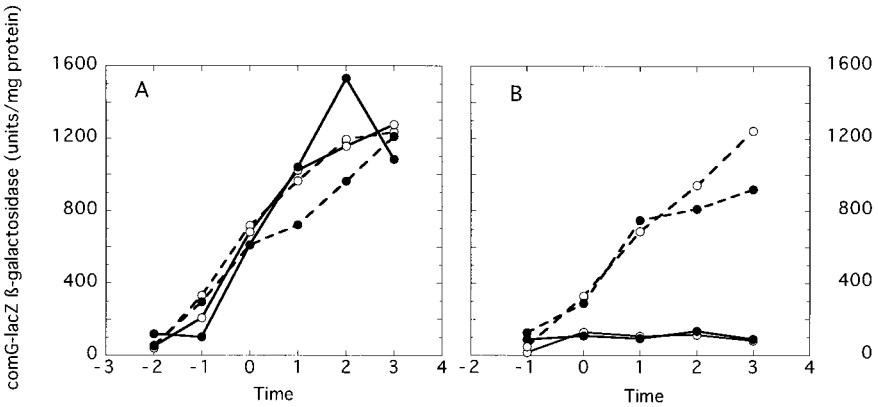

FIG. 3. Expression of *comG-lacZ* in Δ*mecA*::*erm Pspac-abrB* strains in the presence of 0.025 (A) and 2 (B) mM IPTG. Dashed lines, results obtained in the absence of IPTG; solid lines, results obtained in its presence. The strains used were *Pspac-abrB*(*spc*) Δ*abrB*::*cat* Δ*mecA*::*erm comG-lacZ*(*kan*) (BD2249) (○) and *Pspac-abrB*(*spc*) Δ*abrB*::*cat* Δ*mecA*::*erm spo0AΔ204 comG-lacZ*(*kan*) (BD2313) (●).

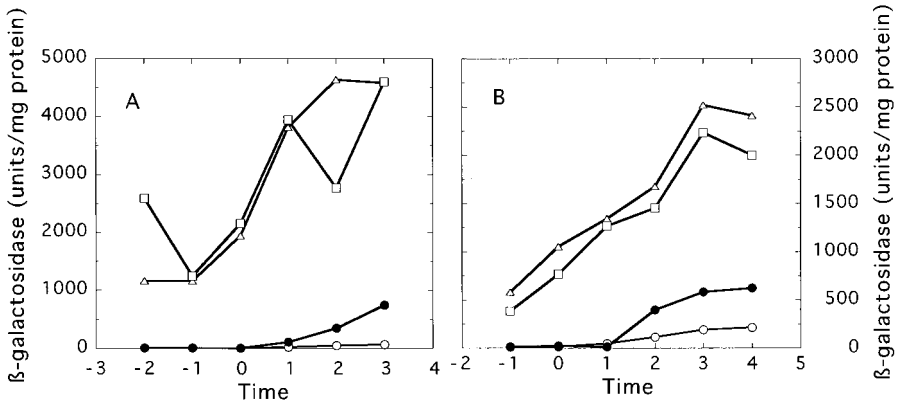

FIG. 4. Expression of *comG-lacZ* (A) and *comK-lacZ* (B) in Δ*mecA*::*erm* Δ*abrB*::*cat* strains. The strains used were *comG-lacZ*(*kan*) (BD1959) or *comK-lacZ*(*spc*) (BD2180) (●), *comG-lacZ*(*kan*) Δ*abrB*::*cat* (BD2374) or *comK-lacZ*(*spc*) Δ*abrB*::*cat* (BD2245) (○), *comG-lacZ*(*kan*) Δ*mecA*::*erm* (BD2376) or *comK-lacZ*(*spc*) Δ*mecA*::*erm* (BD2377) (△), and *comG-lacZ*(*kan*) Δ*abrB*::*cat* Δ*mecA*::*erm* (BD2376) or *comK-lacZ*(*spc*) Δ*abrB*::*cat* Δ*mecA*::*erm* (BD2378) (□).

pression of *comG-lacZ* and *comK-lacZ* in Δ*abrB*::*cat* Δ*mecA*::*spc* strains was analyzed (Fig. 4). Although higher levels of both fusions were expressed in the *mecA* background, the synthesis of β-galactosidase was still growth stage regulated. Therefore, the additional regulatory mechanism does not require MecA or AbrB and affects the level of *comK* expression. The gene(s) mediating this mechanism is unknown.

Why is ComK synthesis controlled by redundant mechanisms? When ComK is overexpressed, nucleoid separation is impaired (11) and colony-forming ability decreases. Therefore, redundant control mechanisms may prevent inappropriate, catastrophic expression of *comK*.

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