Transient gene asymmetry during sporulation and establishment of cell specificity in *Bacillus subtilis*

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Sporulation in *Bacillus subtilis* is initiated by an asymmetric division generating two cells of different size and fate. During a short interval, the smaller forespore harbors only 30% of the chromosome until the remaining part is translocated across the septum. We demonstrate that moving the gene for σF, the forespore-specific transcription factor, in the trapped region of the chromosome is sufficient to produce spores in the absence of the essential activators SpoIIAA and SpoIIIE. We propose that transient genetic asymmetry is the device that releases SpoIIIE phosphatase activity in the forespore and establishes cell specificity.

Establishment of cell specificity is a fundamental question in developmental biology that can be addressed by studying primitive differentiation systems such as sporulation in *Bacillus subtilis* [Errington 1996]. In this soil bacterium, starvation induces an asymmetric septation event that leads to the formation of two cells with different fates [Stragier and Losick 1996]. The smaller cell [the forespore] eventually matures into a dormant spore that is released into the medium by lysis of the mother cell. Gene expression in the two cells is controlled by the successive appearance of four new σ factors that modify RNA polymerase promoter specificity. The developmental programs of the two cells are tied to each other such that the whole cascade ultimately depends on the activation of the first transcription factor, σF [Losick and Stragier 1992].

σF, the product of the spoIIGC gene, is synthesized in the predivisional cell together with the two regulatory proteins SpoIIAA and SpoIIIE. As shown in Figure 1, σF is held in inactive form by association with the anti-σ factor SpoIIB [Duncan and Losick 1993; Min et al. 1993]. This interaction is disrupted by the SpoIIAA protein after polar septation has occurred and exclusively in the forespore [Diederich et al. 1994; Duncan et al. 1996]. SpoIIAA is itself inactivated by phosphorylation by the SpoIIAB protein acting as a kinase [Min et al. 1993], whereas active SpoIIAA is regenerated by the SpoIIIE phosphatase [Duncan et al. 1995]. Because SpoIIIE is also synthesized in the predivisional cell, the establishment of forespore genetic identity relies on the mechanisms delaying SpoIIIE-mediated σF activation until after septation and restricting this activation to the forespore.

It has been proposed that accumulation of dephosphorylated SpoIIAA in the forespore is a consequence of the concentration bias between the SpoIIIE phosphatase and the SpoIIAB kinase created by the targeting of SpoIIE to the sporulation septum [Arigoni et al. 1995; Duncan et al. 1995]. Additional observations have led to the suggestion that SpoIIE is sequestered on the forespore side of the septum [Wu et al. 1998] or, alternatively, that a putative inhibitor of SpoIIIE is excluded from the forespore [Arigoni et al. 1999].

Interestingly, the asymmetric cell division occurring at the beginning of the sporulation process in *B. subtilis* is accompanied by a transient genetic asymmetry. Because of the extended structure of the DNA in the predivisional cell, the sporulation septum bisects one of the two chromosomes and only about 30% of the genetic material is initially trapped into the forespore compartment (Fig. 2A). The remaining part of the chromosome is transferred into the forespore by a process requiring the SpoIIIE DNA translocase located at the center of the septum [Wu et al. 1995; Wu and Errington 1997]. A fixed region of the chromosome, the 30% surrounding the replication origin (Fig. 2B), is always enclosed in the forespore [Wu and Errington 1998] and constitutes its sole genetic material for an interval estimated to 10–15 min [Pogliano et al. 1997]. We wondered whether this brief genetic difference between the two cells could be involved in establishing forespore specificity. To address this question, we designed artificial conditions to see whether this transient gene asymmetry could be sufficient to trigger cell differentiation.

![Figure 1](https://genesdev.cshlp.org/)

**Figure 1.** The σF regulatory pathway. σF is unable to interact with core RNA polymerase when bound to SpoIIAB, in the pre-divisional cell and in the mother cell [Duncan and Losick 1993; Min et al. 1993]. SpoIIAB can release σF by binding SpoIIAA in the forespore [Diederich et al. 1994; Duncan et al. 1996]. SpoIIAA cannot bind SpoIIAB when phosphorylated by SpoIIAB acting as a kinase [Min et al. 1993]. Active SpoIIAA is regenerated by the SpoIIIE phosphatase [Duncan et al. 1995] in the forespore [Lewis et al. 1996]. Arrows indicate activation, and T-headed arrows indicate inhibition.

[Key Words: Bacillus subtilis; sporulation; septum; asymmetry; SpoIIE; σF]
Results

Activating \( \sigma^F \) without SpoIIAA

The three proteins SpoIIAA, SpoIIAB, and \( \sigma^F \) are encoded by the spoIIA operon located at 209° on the 360° genetic map of B. subtilis, far from the replication origin located at 0° (Fig. 2B). Because of the physical interactions between these proteins (Fig. 1), they have to be synthesized in stoichiometric amounts to ensure normal regulation of \( \sigma^F \) activity. We reasoned that moving spoIIAC, the gene encoding \( \sigma^F \), to the region of the chromosome initially trapped in the forespore, and leaving spoIIAB at its normal location, would allow transient accumulation of \( \sigma^F \) in the forespore while synthesis of new SpoIIAB molecules would be confined to the mother cell. Then, if the asymmetric distribution of the forespore chromosome lasts long enough, the imbalance generated in favor of \( \sigma^F \) in the forespore could be such that some of the \( \sigma^F \) molecules would escape inhibition by SpoIAB, without requiring SpoIIAA counteracting SpoIAB.

A series of strains was constructed in which the spoIIA gene was inactivated by an in-frame deletion, the spoIIAC gene at the spoIIA locus was disrupted, and the spoIIAC gene under the control of the spoIIA promoter was integrated at various locations on the chromosome, mostly through insertion into a Tn917 transposon, as detailed in Materials and Methods. [Ectopic expression of spoIIAC at all loci appeared normal as judged from complementation of the spoIIAC defect of an otherwise wild-type strain]. These strains were grown in sporulation medium, and the number of heat-resistant spores produced was determined. A typical series of results is shown in Figure 3. Whereas inactivation of the spoIIA locus normally creates a complete block in sporulation (<10 spores/ml instead of \( 2 \times 10^8 – 5 \times 10^8 \) in wild-type cells), a very high number of spores (\( 5 \times 10^6 – 10^7 \) spores/ml) was observed when the spoIIAC gene was located in the 300°–40° interval. This location fits very well with the region that is trapped in the forespore by asymmetric septation (Wu and Errington 1998), and it suggests that the bypass of the SpoIIAA product for \( \sigma^F \) activation is due to the transient accumulation of \( \sigma^F \) in the forespore in the absence of the spoIIAB gene, resulting in titration of SpoIAB by \( \sigma^F \). A much lower but still significant amount of spores (\( 10^4 – 10^5 \) spores/ml) was observed when spoIIAC was located outside of the 300°–40° interval and, therefore, was assumed to be always present in the same cell as spoIIAB. It might be that physically separating the spoIAB and spoIIAC genes creates a slight imbalance in favor of \( \sigma^F \), either because

![Figure 2](image-url)  
Figure 2. [A] Forespore chromosome partitioning [Wu et al. 1995, Wu and Errington 1997]. The two chromosomes issued from the last round of replication are in an extended structure in the predivisional cell [top]. A septum is laid down close to one pole and bisects one of the chromosomes, creating transient gene asymmetry [middle]. The remaining part of the chromosome is then translocated across the septum into the forespore [bottom]. [B] Map of the chromosome indicating the approximate borders (dotted lines) of the region surrounding the replication origin [oriC] initially trapped in the forespore [Wu and Errington 1998]. The positions of the spoIIA and spoIIE loci are indicated.

![Figure 3](image-url)  
Figure 3. Spore formation in the absence of SpoIIAA. A series of strains deleted for spoIIA, and in which spoIIAC was inactivated at the spoIIA locus and inserted at various locations around the chromosome, were grown in sporulation medium for about 30 hr, and heat-resistant spore numbers were determined. The experiment was done at least twice and, for most strains, three times. Very similar results were obtained in each case. A typical series of results is shown.
of higher synthesis of $\sigma^F$ from the altered spoIIA gene, or because interaction between SpoIIB and $\sigma^F$ is more efficient when they are synthesized in the immediate vicinity of each other. Alternatively, short segments of the chromosome located outside of the 30% surrounding the replication origin might occasionally be trapped in the forespace during asymmetric septation and the spoIIA gene segregated away from spoIIB.

The progress of sporulation in one of the strains in which SpoIIA could be efficiently bypassed was studied further by electron microscopy. As reported in Table 1, about half of the bacteria harvested 4 hr after the entry into stationary phase showed the classic disporic phenotype of spoIIA mutants, with forespores at both ends of the cells. However, 14% of the cells had reached the morphological stage where the forespace is fully engulfed by the mother cell, a step that is absolutely dependent on $\sigma^F$ [Londoño-Vallejo et al. 1997]. This suggests that the efficiency of $\sigma^F$ activation might be even higher than indicated by the 2%-4% of mature heat-resistant spores produced by that strain and that, in many cells, sporulation aborts later because of some unidentified deficiency, possibly by unregulated SpoIIB interfering with $\sigma^F$, the late forespace $\sigma$ factor [Kellner et al. 1996]. Direct measurement of $\sigma^F$ activity indicated that the rate of accumulation of $\beta$-galactosidase synthesized under the control of a $\sigma^F$-dependent promoter was about 10% of that observed in wild type, a result that did not depend on the location of the reporter gene on the chromosome (data not shown).

**Activating $\sigma^F$ without SpoIIE**

The SpoIIE protein has been described as a bifunctional protein, acting as a phosphatase on phosphorylated SpoIIA molecules, as well as being required for maturation of the sporulation septum [Barák and Youngman 1996; Feucht et al. 1996]. Null mutations in spoIIE completely prevent spore formation. Because the presence of spoIIA in the replication origin region allowed a significant number of cells to bypass the normal regulatory pathway of $\sigma^F$ activation and to sporulate without production of dephosphorylated SpoIAA, we checked the effect of the absence of SpoIIE in these conditions. Strains were constructed in which the spoIIE and spoIIAC loci were disrupted, and the spoIIAC gene under the control of the spoIIA promoter was introduced at various locations on the chromosome. We found that the presence of the spoIIAC gene at 18°, 33°, and 317° allowed spore production without SpoIIE in the same range as in strains bypassing SpoIIA [7 x 10^7–2 x 10^7 spores/ml]. Moreover, electron microscopy analysis revealed that, in addition to the 30% of cells showing the classical spoIIA null phenotype (thick septa and multiple septa), 17% of the cells had completed engulfment 4 hr after the entry into stationary phase (Table 1), suggesting that SpoIIE can be as efficiently bypassed as SpoIIA for spore morphogenesis. Finally, introduction of a spoIIE mutation in strains engineered to bypass SpoIIA and harboring the spoIIA gene at 28° or 337° did not alter significantly their efficiency of sporulation [about 1 x 10^7 spores/ml].

We took advantage of the possibility to bypass SpoIIE for $\sigma^F$ activation to investigate more about the molecular mechanisms underlying this phenomenon. The spoIIA and spoIIAC genes of a spoIIE null mutant were both disrupted and moved to separate positions on the chromosome. The spoIIA gene, under the control of the spoIIA promoter and together with the spoIIAA gene, was inserted at 324°, a chromosomal location that is trapped in the forespace during asymmetric septation. The spoIIAC gene, under the control of the spoIIA promoter, was introduced at positions that are segregated either inside (33° or 317°) or outside (172° or 194°) the forespace. None of these strains produced any spores, indicating that, for bypassing the regulatory pathway activating $\sigma^F$, separating the spoIIA and spoIIAC genes is not sufficient and that spoIIA has to be initially located outside the forespace.

The identity of the chromosomal segment trapped in the forespace [Fig. 2B] has been described to be dependent on the product of the spo0J gene that would anchor the chromosome to the cell pole before division [Sharpe and Errington 1996]. Therefore, we inactivated the spo0J locus in the spoIIE strains harboring spoIIA at 324° and spoIIA at 172° or 194°. We expected that in a significant number of cells, the spoIIAC gene would be trapped in the forespace whereas the remote spoIIA gene would remain in the mother cell and that heat-resistant spores would be produced. However, this was not the case and neither strain was able to produce a single spore, suggesting that the chromosomal region around 324° is always trapped in the forespace, even in the absence of the SpOJ protein. It is unlikely that this complete absence of spore production [as compared to the 5 x 10^6–10^7 spores/ml observed in the previous set of experiments] is due to an abnormally high level of expression of spoIIA at 324°.

### Table 1. Phenotypic classes scored by electron microscopy

| Morphological characteristics | Wild type | SpoIIA bypass^a | SpoIIE bypass^b |
|------------------------------|-----------|-----------------|-----------------|
| No septum                    | 25        | 14              | 29              |
| Central septum               | 3         | 0               | 6               |
| Thin septum                  | 8         | 20              | 13              |
| Thick septum                 | 0         | 0               | 20              |
| Multiple septa               | 0         | 3               | 9               |
| Disperses                    | 0         | 49              | 6               |
| Engulfed forespores          | 64        | 14              | 17              |

Values are expressed as percentage of each phenotype in cells harvested 4 hr after the onset of sporulation.

^aThe strain contains an in-frame deletion in spoIIA and an erythromycin resistance cassette in spoIIB, whereas an intact copy of spoIIA is inserted at 317° through the zii83::Tn917 transposon.

^bThe strain contains a phleomycin resistance cassette in spoIIB and an erythromycin resistance cassette in spoIAC, whereas an intact copy of spoIIAC is inserted at 317° through the zii83::Tn917 transposon.
Discussion

The importance of transient gene asymmetry

The regulatory pathway controlling $\sigma^F$ activity involves three proteins, SpoIIE, SpoIIAA, and SpoIIAB, and is intimately tied to completion of septum formation. Its complexity seems to be a prerequisite for preventing $\sigma^F$ activation in the predivisional cell, which would block further progression of the sporulation process (Coppolecchia et al. 1991), as well as for relaxing $\sigma^F$ inhibition exclusively in the forespore. Here, we report that most of this pathway can be partially bypassed just by displacing the gene encoding $\sigma^F$ on the chromosome and that the SpoIAB protein may be sufficient to control $\sigma^F$ activity such that sporulation occurs with 2%-4% of wild-type efficiency. Because a large portion of the chromosome is segregated into the forespore only after septation, unequal division of the sporulating cell creates a transient gene asymmetry that lasts long enough to establish forespore genetic specificity, providing that the genes encoding $\sigma^F$ and its SpoIAB inhibitor are located in appropriate regions of the chromosome.

An unexpected result of these experiments is that there is no significant difference in sporulation efficiency between cells engineered to bypass SpoIIAA, the antagonist of SpoIAB, and cells engineered to bypass SpoIIE, the protein activating SpoIIAA. This suggests that the only essential role of SpoIIE in sporulation is to allow formation of active, dephosphorylated SpoIIAA, although it has been described as also being required for septum formation and maturation (Barik and Youngman 1996; Feucht et al. 1996). Electron microscopy studies of bacteria bypassing SpoIIE have confirmed the presence of many cells with abnormally thick septa or multiple septa (which become a prominent feature in cells harvested at later times), whereas bacteria bypassing SpoIIAA showed only thin septa. However, because 30% of the cells bypassing SpoIIE contained either a thin septum or a fully engulfed forespore (Table 1), it appears that the involvement of SpoIIE in septum maturation is indirect and accessory.

Another side result of these experiments is that the Spo0J protein is not involved in specifying the orientation of the chromosome and thus defining the region that is initially trapped in the forespore, as proposed previously (Sharpe and Errington 1996). Because of the remarkable sensitivity of the sporulation assay (six orders of magnitude in our bypass experiments), it can be concluded that the region surrounding 324° is always on the forespore side after asymmetric septation, even in the absence of Spo0J. However, if Spo0J is involved in chromosome organization (Lin and Grossman 1998), its absence might allow additional short DNA segments located outside of the 30% surrounding the replication origin to be trapped in the forespore at a significant frequency, as suggested previously [Webb et al. 1997]. Indeed, the main evidence for a centromere-like function of Spo0J was the demonstration that the absence of Spo0J allows some expression of a $\sigma^F$-dependent reporter gene located in a region of the chromosome normally excluded from the forespore in a strain blocked in the chromosomal translocation process (Sharpe and Errington 1996).

A model for establishment of forespore specificity

The experiments described above indicate that the transient gene asymmetry existing after polar division can create an imbalance between two proteins (in our artificial conditions $\sigma^F$ and SpoIIAB) sufficient to switch on the forespore genetic program in a significant number of cells. We propose that this regulatory device is naturally occurring, acting at the level of the SpoIIE protein. The mechanisms allowing accumulation of dephosphorylated SpoIIAA molecules specifically in the forespore are still a matter of conjecture. The ratio between the two enzymes acting on SpoIIAA in opposite directions, the SpoIAB kinase and the SpoIIE phosphatase, has been suggested to play a crucial role (Duncan et al. 1995). Therefore, it is intriguing that the genes encoding these two proteins are located at such chromosomal positions (Fig. 2B) that asymmetric septation will effectively create a bias in favor of SpoIIE in the forespore. However, displacing the spoIIIE gene at 283°, outside of the region trapped in the forespore, has no effect on sporulation efficiency [F. Arigoni and N. Frandsen, unpubl.], suggesting that additional synthesis of SpoIIIE in the forespore is not important for activating $\sigma^F$.

It has been proposed recently that SpoIIE phosphatase activity is controlled by an inhibitory molecule that is specifically excluded from the forespore (Arigoni et al. 1999). Transient gene asymmetry could be the basis of this exclusion if the SpoIIE inhibitor is an unstable protein encoded by a gene located outside of the chromosome interval trapped in the forespore (Fig. 4). In that case, the imbalance between the two partners would result from depletion of the inhibitor in the forespore (instead of accumulation of its target protein as in our experiments above), whereas SpoIIE would be kept inactive.

![Figure 4](genesdev.cshlp.org)

Figure 4. How transient gene asymmetry could activate SpoIIE. The SpoIIE molecules (ovoids) are targeted to the sporulation septum, which bisects one of the two chromosomes (wiggly lines). The SpoIIE molecules are locked in inactive form (shaded ovoids) by interaction with an inhibitor [T-shaped, solid] encoded by a gene [solid circles and arrows] located on the mother-cell side [left] of the septum. In the forespore [right] the inhibitor is not neosynthesized and disappears [T-shaped, open], switching some SpoIIE molecules to an active form (solid ovoids).
in the mother cell by continued synthesis of its inhibitor. Escaping inhibition would allow some SpoIIIE molecules to activate SpoIIAA and ultimately to activate $\sigma^F$. Because of the catalytic activity of SpoIIIE, a partial and transitory release of its inhibition could be sufficient to induce an irreversible switch in forespore gene expression before the entry of the remaining part of the forespore chromosome. Other models are possible but our results suggest that the transient genetic asymmetry resulting from the polar position of the sporulation septum could be the signal triggering the forespore fate.

Material and methods

Bacterial strains

All the results reported in this paper were obtained with derivatives of the sporulation-proficient strain JH642 [trpC2 pheA1]. The in-frame deletion in sporIIA originates from strain JIC5Adel1 kindly provided by M. Yudkin (Min et al. 1993). It was transferred into the JH642 background by linkage with a kanamycin-resistance marker inserted between the spoIIA and spoIVA operons (F. Arigoni, unpublished). The spoIAC null mutant was created by insertion of an erythromycin-resistance marker at codon 127 of spoIIA. The spoIIAB spoIAC double mutant was created by insertion of an erythromycin-resistance marker between codon 87 of spoIIAB and codon 127 of spoIIA. The spoIIA null mutant tagged with a phleomycin-resistance marker has been described (Arigoni et al. 1999). The spoIAC mutant was constructed by A.-M. Guérout-Fleury via insertion of a kanamycin-resistance marker between codon 21 of soj and codon 190 of spoI (inactivation of the adjacent soj gene suppresses the early sporulation blockage observed in the absence of SpoO) [Ireten et al. 1994]). The spoIIA spoIAC deletion fusion used as a reporter of $\sigma^F$ activity has been described (Shazand et al. 1995) and was inserted at the amyE or the thrC locus (Guérout-Fleury et al. 1996) through linkage to a tetracycline-resistance marker. Conditions of selection for antibiotic resistance and of sporulation by exhaustion of Difco nutrient broth medium have been described (Arigoni et al. 1999).

Ectopic expression of segments of the spoIIA operon

The proximal region of the spoIIA operon, from the 5' end site located 165 bp upstream of the spoIIA transcription start to the PvuII site located at codon 13 of spoIIA, was inserted in the nonessential ywlB gene by linkage to a spectinomycin-resistance marker, allowing expression of spoIIA and spoIIAB from position 324° on the chromosome. The in-frame deletion overlapping spoIIA and spoIIAB and placing spoIIA alone under the control of the spoIIA promoter has been described (Shazand et al. 1995). This construct was linked to a chloramphenicol-resistance marker (upstream and diverging from spoIAC) and to the strong transcription terminators t53 from rnb8 (downstream from and converging toward spoIAC) and inserted between positions 1093 and 2507 of Tn917, spoIIA being in the opposite orientation of the inactivated erythromycin-resistance marker. It was introduced at various locations on the chromosome by transformation of a collection of strains, each harboring a specific Tn917 insertion. The following strains (all from the Bacillus Genetic Stock Center) were used [location of the Tn917 insertion is indicated]: A686 [zea-86, 18°], A2724 [zhu-88, 33°], A628 [zby-82, 75°], A630 [zez-82, 94°], A631 [zzd-85, 123°], A635 [zez-82, 172°], A637 [zff-62, 194°], A639 [zgg-83, 245°], A643 [zbg-82, 294°], A644 (zby-83, 317°), A732 [zid-89, 337°], A645 [zif-85, 345°]. In six cases, the left border of the Tn917 insertion was amplified by reverse PCR and sequenced, indicating differences of $\sigma^F$ with the genetically determined chromosome positions of the Tn917 insertions (Youngman 1993). The same spoIIA fragment was also introduced at the amyE (28°) and thrC (283°) loci (Guérout-Fleury et al. 1996).

Ultrastructural studies

Samples for electron microscopy were processed as described previously (Arigoni et al. 1999). Stained thin sections were examined and photographed on a JOEL-100 CX electron microscope. For quantification of morphological classes, at least 100 complete longitudinal sections were scored from random fields for each sample.

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