Linking asymmetric division to cell fate: teaching an old microbe new tricks

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Understanding the connection between cell division and cell fate is a fundamental challenge in developmental biology. In organisms ranging from microbes to mammals, cell division can give rise to progeny cells that differ in fate from one another. In some cases, cell specificity is imposed by external cues that differentially influence the fate of the progeny cells. In other cases, specificity is established by an intrinsic asymmetry in the progenitor cell [Horvitz and Herskowitz 1992]. In such cases, cell specificity is frequently attributed to the preferential segregation of a cell-fate determinant to one progeny cell. Thus, in Drosophila melanogaster, the cell-fate determinants Numb and Prospero differentially localize to the basal side of the dividing neuroblast, with Prospero doing so in a manner that depends on the localization of another protein [Miranda] to the basal cortex [Hawkins and Garriga 1998]. Likewise, in the budding yeast Saccharomyces cerevisiae, the distinct fate of the newborn cell [an inability to undergo a switch in mating type] is determined by the transport into the bud prior to cytokinesis of the mRNA for a repressor protein [ASH1p] that prevents mating type switching [Long et al. 1997; Takizawa et al. 1997]. The subject of this review is Bacillus subtilis, a spore-forming bacterium in which a visibly asymmetric process of cell division gives rise to progeny cells that differ in fate from one another as well as from the progenitor cell. Here too, as we shall see, the subcellular distribution of a cell-fate determinant [a serine phosphatase known as SpoIIE] is involved in the establishment of cell fate. As reported in this issue, Frandsen et al. [1999] have, however, cleverly taught B. subtilis the trick of sporulating in a manner that bypasses the SpoIIE determinant. Taking advantage of an idiosyncratic feature of chromosome segregation during asymmetric division, these workers have devised a mechanism of cell specification that is dictated by the asymmetric distribution of a gene, rather than the localization of a protein.

A hallmark of entry into sporulation is the formation of an asymmetrically positioned [polar] septum that divides the developing cell or sporangium into dissimilar-sized progeny cells [Piggot and Coote 1976; Stragier and Losick 1996]. These are the forespore [the smaller cell] and the mother cell [so named because it will nurse the developing spore]. Each progeny cell receives a chromosome from the last round of vegetative DNA replication, but the forespore does so in an unusual manner. In both prokaryotes and eukaryotes, chromosome segregation normally precedes cytokinesis, newly duplicated chromosomes separate from each other and the cell is divided in two by cytokinesis. In sporulation, however, the reverse is true [Wu and Errington 1994, 1998; Wu et al. 1995]. The polar septum is formed prior to the incorporation of a complete chromosome into the forespore cell. Instead, only about one-third of the chromosome is present [trapped] in the forespore at the time of polar septation, the remaining two-thirds is translocated across the septum into the forespore after cytokinesis [Fig. 1]. This process depends on the SpoIIE protein, which is located in the septum [Wu and Errington 1997], in which it could form a channel or serve as a DNA translocase or both. Interestingly, the region of the chromosome that is initially trapped in the forespore is not random but rather that portion of the chromosome that is proximal to the origin of replication. This was inferred from the pattern of expression of genes whose transcription is under the control of transcription factor $\sigma^F$, which is active exclusively in the forespore [more about $\sigma^F$ presently]: in a spoIIE mutant only $\sigma^E$-controlled genes located proximal to the origin of replication are expressed [Sun et al. 1991; Wu and Errington 1994, 1998; Wu et al. 1995]. Subsequent work demonstrated that early in sporulation the origin regions of the two chromosomes are located near opposite poles of the sporangium so that when asymmetric division takes place only the origin-proximal region is trapped in the forespore [Glaser et al. 1997; Lin et al. 1997; Webb et al. 1997]. Indeed, movement of origins toward opposite poles of the cell has emerged as a general feature of chromosome segregation during the vegetative cell cycle of B. subtilis [Glaser et al. 1997; Lin et al. 1997; Webb et al. 1997, 1998], as well as that of other bacteria [Gordon et al. 1997; Mohl and Gober 1997].

Once created by polar division, the mother cell and the forespore follow dissimilar programs of gene expression, which are set in motion by the transcription factors $\sigma^E$ and $\sigma^F$ [for review, see Stragier and Losick 1996]. Both
where it undergoes conversion to mature
at the polar septum (Ju et al. 1997; Hofmeister 1998),
during asymmetric division it comes to localize
associated with the cytoplasmic membrane (Hofmeister
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of the two regulatory proteins becomes compartmental-
formation of the polar septum? Interestingly, the action
of the membrane protein SpoIIGA, which is likely
to be the processing enzyme and which is itself located
in the polar septum (Fawcett et al. 1998). SpoIIGA is
inactive in its default state. For SpoIIGA to bring about
the processing of pro-σE, the protease must be activated
by a signaling protein called SpoIIR, which is produced in
the forespore under the control of σE (Hofmeister et al.
1995; Karow et al. 1995; Londoño-Vallejo and Stragier
1995, Shazand et al. 1995). SpoIIR is a secreted protein
that is believed to interact with SpoIIGA in the intraspe-
tal space between the mother cell and forespore mem-
branes. If so, SpoIIGA can be thought of as a receptor/
protease.

This intercompartmental signaling pathway is a tim-
ing device [Driks and Losick 1991; Margolis et al. 1991;
Zhang et al. 1996]. It delays the processing of σE until
after asymmetric division by tying the activity of the
SpoIIGA protease to σE, whose activation, as we shall
see, is itself linked to the formation of the polar septum.
A separate, and as yet not well understood, pathway is
responsible for limiting σE protein to the mother cell
following the formation of the polar septum [Zhang et al.
1996; Pogliano et al. 1997; Ju et al. 1998].

What is the nature of the mechanism that restricts σE
activity to the forespore compartment of the sporan-
gium? The activity of σE is governed by a three-protein
pathway [Stragier and Losick 1996 and references
therein] consisting of SpoIIE, a serine phosphatase [Dun-
can et al. 1995], SpoIIA, an anti-anti-σ factor [Alper
et al. 1994; Diederich et al. 1994], and SpoIIAB, a dual-func-
tion protein that is both an anti-σ factor [Duncan and
Losick 1993] and a serine kinase [Min et al. 1993]. In brief
(and to oversimplify; see Fig. 1), SpoIIAB holds σE in
an inactive complex in the predivisional sporangium and in
the mother cell. In the forespore, σE escapes from the
SpoIIAB-σE complex and is free to associate with core
RNA polymerase and direct transcription. This escape
occurs by a reaction in which the anti-anti-σ factor
SpoIIA attacks the SpoIIAB-σE complex, causing the
release of free σE. SpoIIA exists in two states: a phos-
phorylated state [SpoIIA-P], which is generated by the
anti-σ factor/kinase SpoIIAB, and an unphosphorylated
state [SpoIIA], which is generated by the action of the
serine phosphatase SpoIIE. Only unphosphorylated
SpoIIA is capable of reacting with SpoIIAB-σE to
cause the release of σE. A key and still unsolved aspect of
the forespore-specific activation of σE is the question of
how the opposing action of the kinase and phosphatase lead
to the preferential accumulation of unphosphorylated
SpoIIA in the forespore.

Evidence suggests that both SpoIIE and SpoIIAB are
subject to regulatory inputs that contribute to the cell-
specific activation of σE [Alper et al. 1994; Arigoni et al.
1995, 1999; Levin et al. 1997; Garsin et al. 1998]. One
of these inputs [the only one we consider here] is the asso-
ciation of SpoIIE, which contains 10 apparent mem-
brane-spanning domains in its amino-terminal region
(Arigoni et al. 1999), with the polar septum [Arigoni et al.
1995]. Cytokinesis in bacteria is mediated by the tubu-
lin-like protein FtsZ, which polymerizes into a ring (the
Z ring) at the future site of cell division. In sporulating
bacteria, the site of Z-ring formation switches from the
mid-cell position to sites near both ends of the sporan-

Figure 1. Chromosome segregation and cell-specific activation of σE and σF. Early in sporulation [top left], the origin regions
[purple] of the newly replicated chromosomes are located near
opposite poles of the predivisional sporangium. Formation of
the polar septum [middle left] initially traps the origin–proxi-
mal third of the chromosome in the forespore. Subsequently
[bottom left], the remaining two-thirds of the chromosome is
translocated into the forespore. Contemporaneously with these
events [see the text], the σE and σF factors, which are in inactive
states in the predivisional sporangium [top right], become active
[red] in a cell-specific manner [bottom right]. AB-σF, AA-AB, and
AA-P refer to SpoIIAB-σF, SpoIIAA–SpoIIAB, and SpoIIAA–P,
respectively. The orange bar indicates the septal localization of
the SpoIIE phosphatase.

regulatory proteins are produced and present in the pre-
divisional sporangium, but they do not become engaged
in directing gene transcription until after asymmetric
division when σF turns on transcription in the mother
cell and σE does so in the forespore [Fig. 1]. Why are
σE and σF inert prior to asymmetric division, and how do
they become active in a cell-specific fashion after the
formation of the polar septum? Interestingly, the action
of the two regulatory proteins becomes compartmental-
ized by completely unrelated mechanisms. Yet in both
cases the polar septum, which can perhaps be thought of
as an organelle for the establishment of cell fate, is inti-
mately involved.

Activation of σE in the mother cell appears to be the
composite consequence of two pathways of regulation
(Stragier and Losick 1996 and references therein). One
pathway operates at the level of the proteolytic process-
ing of an inactive precursor to σE called pro-σE, which
harbors an amino-terminal extension of 27 residues.
Pro-
σE is present in the predivisional sporangium, where it
is associated with the cytoplasmic membrane [Hofmeister
1998]. During asymmetric division it comes to localize
at the polar septum [Ju et al. 1997; Hofmeister 1998],
where it undergoes conversion to mature σE due to the
action of the membrane protein SpoIIGA, which is likely
to be the processing enzyme and which is itself located
in the polar septum (Fawcett et al. 1998). SpoIIGA is
gium (Levin and Losick 1996). One (and normally only one) of the two polar Z rings is used for the formation of a septum. SpoIIIE colocalizes with the bipolar Z rings, generating thereby E rings (Levin et al. 1997). During cytokinesis, SpoIIIE at the site of asymmetric division invades and becomes part of the polar septum. This is essential for the activation of $\sigma^F$ because in sporangia that have been deprived of FtsZ, SpoIIIE fails to localize and $\sigma^F$ is not activated (Levin et al. 1997). This finding is significant because it indicates the existence of an explicit link in the chain of biochemical events from asymmetric division to the activation of $\sigma^F$.

But how does localization of the SpoIIIE phosphatase to the polar septum contribute to the compartmentalization of $\sigma^F$ activation? Three models have been considered. In one model SpoIIIE is displayed equally on both faces of the polar septum, but because of the extreme asymmetric placement of the septum, the ratio of phosphatase to kinase is higher in the forespore than in the mother cell, thereby favoring the preferential accumulation of unphosphorylated SpoIIP in the smaller chamber of the sporangium (Arigoni et al. 1995, 1996). A second model is that SpoIIIE is on both faces of the septum but active only on the forespore face (Arigoni et al. 1995, 1999), and yet a third model is that SpoIIIE is sequestered to the forespore face of the septum (Feucht et al. 1996; Wu et al. 1998). Wu et al. (1998) have argued in favor of the sequestration model on the basis of experiments in which SpoIIIE that had been tagged with green fluorescent protein (GFP) was released from the septum by treatment of sporangia with lysozyme. Under such conditions, fluorescence was more intense in the resulting forespore protoplast than in the mother cell protoplast, however, significant fluorescence was still present in the mother cell protoplasts. In any event, whether SpoIIIE is more concentrated, selectively active, or sequestered to the forespore, we can think of it as a cell-fate determinant that exerts its influence preferentially in one progeny.

It will be clear from the above discussion that although there is much that we still do not understand, the SpoIIIE phosphatase and the SpoIIP anti-anti-$\sigma$ factor play an essential role in the cell-specific activation of $\sigma^F$. It is against this backdrop that the cleverness of the report by Frandsen et al. (1999) should be appreciated for they have created a strain, in fact a series of strains, that entirely lack the gene for SpoIIIE or for SpoIIP and yet are capable of producing spores. They have substituted the asymmetric distribution of the SpoIIIE determinant with the asymmetric distribution of the gene for $\sigma^F$ by a strategy that exploits the fact that during sporulation chromosome segregation largely takes place after cytokinesis. As we have seen, following asymmetric division only the origin-proximal one-third of the forespore chromosome is present initially in the forespore. The remainder of the chromosome must be translocated across the septum after cytokinesis. Thus, for a period of several minutes, the origin-proximal portion of the chromosome is present in the forespore and the origin-distal portion is not. Frandsen et al. (1999) capitalized on the transient genetic asymmetry by moving the gene for $\sigma^F$, but not the gene for SpoIIIP, from its normal location to each of thirteen sites at scattered locations around the chromosome. Normally, both genes are located near the terminus of replication (Fig. 2). Not unexpectedly, a strain in which the gene for $\sigma^F$ has been moved to any of these locations sporulates normally. However, when the cells are deprived of SpoIIIE or SpoIIP, those strains, and only those strains, that harbor the $\sigma^F$ gene in the origin-proximal region of the chromosome are capable of sporulating (Fig. [2]). Frandsen et al. (1999) suggest that the transient genetic asymmetry of having the gene for $\sigma^F$ present in the forespore in the absence of the gene for its nemesis SpoIIIP results in $\sigma^F$ molecules being synthesized without the corresponding synthesis of the anti-$\sigma$ factor. This leads to a burst of $\sigma^F$ activity exclusively in the forespore that persists at least until the time that the gene for SpoIIIP is finally dragged into the forespore. That is, the asymmetric distribution of a protein (SpoIIIE) has been replaced by the asymmetric distribution of a gene.

What is the biological significance of this finding? Obviously, transient genetic asymmetry of the $\sigma^F$ gene is not the normal basis for the compartmentalization of $\sigma^F$. The origin of replication (ORI) of the chromosome is present initially in the forespore. The remainder of the chromosome is translocated into the forespore. In one of the strains constructed by Frandsen et al. (1999) (right), the gene for $\sigma^F$ has been moved to a location near the origin of replication and is therefore present in the forespore in the absence of the gene for SpoIIIP during the period shortly following the formation of the polar septum. In the strain of Frandsen et al., both the forespore and the mother cell are expected to have SpoIIIP-$\sigma^F$ complexes that were synthesized in the predivisional sporangium. In addition, however, the forespore will transiently synthesize additional $\sigma^F$ molecules without the corresponding synthesis of SpoIIIP molecules. This allows such a strain to sporulate even in the absence of the SpoIIIE phosphatase or the SpoIIP anti-anti-$\sigma$ factor.
activity. But perhaps, as Frandsen et al. (1999) speculate, the gene for a hypothetical inhibitor of the SpoIIIE phosphatase is located in the origin-distal region of the chromosome. If so, for a period of time two copies of the gene would be present in the mother cell and none in the forespore. It will be of much interest to learn whether B. subtilis has been clever enough to exploit transient genetic asymmetry on its own. Have Frandsen et al. taught this old microbe a new trick or one that it knew all along?

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