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Regulation of *fim* genes in uropathogenic *Escherichia coli*

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Abstract

Uropathogenic *Escherichia coli* (UPEC) is the leading cause of urinary tract infections in women, causing significant morbidity and mortality in this population. Adherence to host epithelial cells is a pivotal step in the pathogenesis of UPEC. One of the most important virulence factors involved in mediating this attachment is the type 1 pilus (type 1 fimbria) encoded by a set of *fim* genes arranged in an operon. The expression of type 1 pili is controlled by a phenomenon known as phase variation, which reversibly switches between the expression of type 1 pili (Phase-ON) and loss of expression (Phase-OFF). Phase-ON cells have the promoter for the *fimA* structural gene on an invertible DNA element called *fimS*, which lines up to allow transcription, whereas transcription of the structural gene is silenced in Phase-OFF cells. The orientation of the *fimS* invertible element is controlled by two site-specific recombinases, FimB and FimE. Environmental conditions cause transcriptional and post-transcriptional changes in UPEC cells that affect the level of regulatory proteins, which in turn play vital roles in modulating this phase switching ability. The role of *fim* gene regulation in UPEC pathogenesis will be discussed.

Keywords

Type 1 fimbriae; Type 1 pili; Gene regulation; Uropathogenic *Escherichia coli*; Urinary tract

ROLE OF TYPE 1 PILI IN UROPATHOGENIC *ESCHERICHIA COLI* PATHOGENESIS

Uropathogenic *Escherichia coli* (UPEC) is the number one cause of urinary tract infections in the United States[1,2]. Approximately 6-7 million people are afflicted with a urinary tract infection each year in the United States at a cost of $2.5 billion per year. Urinary tract infections are modeled as ascending infections. In women, the UPEC bacteria move from the rectum to the vaginal surface to the urinary tract. Although UPEC can express several different varieties of pili, type 1 pili may be the most important in the human lower urinary tract. Agglutination of guinea pig erythrocytes in the absence of mannose is an important characteristic of type 1 pili[3,4]. Besides *Escherichia coli* (*E. coli*), type 1 pili are found on several other species within the *Enterobacteriaceae* family[5]. The role of type 1 piliated UPEC cells in the pathogenesis of human urinary tract infections was first demonstrated in the early 1980s and has continued in more recent studies[6-12]. Moreover, these human patient studies have been supported by several murine urinary tract infection model studies that have shown the importance of type 1 pili in UPEC pathogenesis[11,13-15]. This culminated in a study by Connell *et al*[16], who compared a *fimA* mutant strain to the wild-

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type parent to show the critical role of type 1 pili in UPEC colonization of the lower urinary tract.

GENETIC ORGANIZATION OF THE UPEC *fim* OPERON

Type 1 pili are produced from a contiguous DNA segment, labeled the *fim* operon, which encodes the genes necessary for their synthesis, assembly, and regulation. The *fim* cluster was mapped to the 98 min on the *E. coli* chromosome[17]. Nine genes have now been identified within the gene cluster (Figure 1).

The pilin structural gene, *fimA*, encodes a 158-159 amino acid polypeptide with an approximate molecular weight of 17 kDa[18,19]. Immediately upstream of the *fimA* gene is a 314-bp invertible DNA element called *fimS*, which contains the promoter for *fimA* with 9 bp inverted repeats (IRs) flanking this segment of DNA (5′ TTGGGGCCA), labeled IRL and IRR (Figure 1)[20,21]. The *fimA* promoter sequence undergoes site-specific recombination, positioning the invertible element in either the Phase-ON (piliated phenotype) or Phase-OFF (nonpiliated phenotype) orientation. This switching phenomenon is known as phase variation. Two genes upstream of the *fimS* invertible element, *fimB* and *fimE*, encode proteins thought to be involved in positioning the *fimS* DNA and will be discussed further below.

The *fimI* gene was the last gene within the *fim* operon to be characterized[22]. FimI's function is not known. Within the *fim* gene cluster, there are two additional genes involved in transport and assembly of type 1 pili: *fimC* and *fimD*. FimC is a periplasmic chaperone protein[23-25] that helps translocate the fimbrial proteins through the periplasm until the FimC-Fim protein complex reaches the FimD usher. FimD is an integral outer membrane protein that serves as an usher, allowing surface localization of the nascently forming type 1 pilus[26-28].

Although the FimA monomers comprise the bulk of the type 1 pilus structure, FimA does not mediate binding to the mannose containing receptor. An adhesin, encoded by the *fimH* gene, is responsible for this binding[29-33]. The two remaining genes in the *fim* operon are *fimF* and *fimG*. FimF and FimG are associated with FimH adhesin, forming a fibrillum structure that anchors the adhesin to the pilus shaft and controls the length of the type 1 pilus[29,30,34-37].

PHASE VARIATION'S ROLE IN TYPE 1 PILUS EXPRESSION

Phase variation is a reversible process, which, in the case of UPEC, leads to an oscillation between Phase-ON piliated cells and Phase-OFF nonpiliated cells. Using *fimA-lacZ* operon fusions, rates of 10^{-3} to 10^{-4}/cell/generation were originally calculated for type 1 pilus expression[38,39]. Phase variation results in agar and, particularly, broth cultures of UPEC to comprise a mixture of piliated and nonpiliated cells.

The site-specific recombination that allows phase variation to occur requires two trans-acting factors located proximally upstream of *fimS*, encoded by *fimB* and *fimE*[40]. Sequence analysis of *fimB* and *fimE* indicated that the predicted proteins were highly basic, a property of many DNA-binding proteins[41]. The predicted amino acid sequences show homology with the DNA binding domain of integrase[42] and contain a tetrad of conserved amino acids required for the recombinase activity[43-45]. Furthermore, FimB and FimE have 48% amino acid homology with each other[40]. Klemm[40] originally suggested that FimB and FimE might act independently to switch the *fimS* element unidirectionally, either Phase-ON to Phase-OFF or *vice versa*, *via* the two 9 bp invertible repeat elements, IRL and IRR. FimB can bind to the *fimS* element to either switch from Phase-ON to Phase-OFF or vice

versa, with a slight bias towards the Phase-OFF over the Phase-ON orientation (Figure 2)[46-56]. By contrast, FimE binds to switch *fimS* from Phase-ON to Phase-OFF. In rare cases, FimE has been shown to initiate a Phase-OFF to Phase-ON switch[57] or when specific amino acid substitutions are made[45]. Orientation of the *fimS* element in the Phase-OFF position leads to the production of antisense transcripts from the *fimA* promoter[49,58].

FimB-mediated recombination occurs at the rate of 10^{-3} to 10^{-4} per cell per generation that was originally described; however, FimE-mediated switching occurs more often at a frequency of 0.3 per cell per generation[52,59]. Base substitutions within *fimS* demonstrated that FimB and FimE used the same DNA cleavage and religation sites within IRL and IRR, allowing more DNA base variations for FimB than FimE[60]. When *fimB* and *fimE* were provided in *trans* on plasmids, they affected pilin expression, suggesting that the ratio of FimB and FimE is important.

The promoters for both *fimB* and *fimE* have been mapped[61-63]. For the *fimB* gene, the number of promoters varies between one and three. Promoters P1 and P2, which were mapped by Schwan *et al*[63] in two UPEC strains (Figure 1), were confirmed by another group[61]. A potential third *fimB* promoter was also identified by Schwan *et al*[63], approximately 650 bp upstream of the *fimB* P2 promoter, and around 840 bp upstream of the translational start site of *fimB*. This third *fimB* promoter has not been confirmed by other groups and could be an anomaly. It could also be a third *fimB* promoter connected to sialic acid regulation of *fimB* (see below). Certainly, strain differences could explain the different numbers of *fimB* promoters. Only one promoter has been identified for the *fimE* gene[62].

OTHER CO-FACTOR PROTEINS THAT AFFECT PHASE SWITCHING

Besides the *fim* gene cluster, other genes and their gene products contribute to the expression of type 1 pili. Early work mapped a gene, *pilG*, at 27 min on the *E. coli* chromosome that affected inversion of the *fimS* region[21]. A mutation of the *pilG* gene increased the inversion of the *fimS* region by up to 100-fold as measured with a *fimA-lac* fusion[21]. The *pilG* locus was shown to be allelic to *bglY*[64], *drdX*[65], and *osmZ*[66]. Later, it was determined that the *pilG* and *osmZ* genes were in fact alleles of the *hns* gene[66-68]. The *hns* gene encodes the H-NS global regulatory protein[69].

H-NS possibly controls the phase variation of the *fimS* region both directly and indirectly[61,62,70-74]. For a potential direct effect, H-NS binds to sequences adjacent to the *fimS* invertible element[72,75].

Indirectly, H-NS represses the transcription of both *fimB* and *fimE*[62,71,74]. H-NS binds, with a high degree of specificity, to both the P1 and P2 promoter sites for *fimB*[71,72]. The DNA-binding regulatory protein also binds to the *fimE* promoter[71]. Moreover, H-NS also represses *lrp* transcription[76], which would in turn affect the phase switching of the *fimS* element, as described below. Thus, transcriptional repression of the *fimB* and *fimE* site-specific recombinase genes would indirectly influence the position of the *fimS* element, which would indirectly affect phase variation.

Besides H-NS, integration host factor (IHF) and leucine-responsive protein (Lrp) are additional co-factors that affect type 1 pilus phase variation. Both proteins cause sharp bends in the DNA structure, introducing hairpin loops that facilitate recombination events within UPEC. IHF is a two-component protein consisting of IHF encoded by *ihfA*[77] and IHF encoded by *ihfB*[78]. Both Eisenstein *et al*[42] and Dorman *et al*[43] showed that IHF plays a role in type 1 pilus switching. Mutations in either *ihfA* or *ihfB* locked the *fimS* region in either the Phase-OFF or Phase-ON orientation[79]. In both studies, an IHF binding site (IHF

II) proximal to IRR was identified (Figure 3). In addition, an IHF binding site was also identified between IRL and the 3′ end of *fimE* (IHF I)[80]. A mutational analysis of this IHF I site demonstrated that FimB-mediated recombination was more adversely affected, suggesting a directional bias for FimB recombination[73,75,79,81,82].

The leucine-responsive regulatory protein (Lrp) is another protein that has been shown to affect the *fimS* region. Lrp is a global regulator of genes involved in metabolic functions within *E. coli*, including pili synthesis[83]. Mutations of the *lrp* gene cause a lower frequency of recombination of the *fimS* element[80,84]. Lrp binds to three distinct sites within the fimS element that are closer to the IRL site. When the high affinity sites 1 and 2 are mutated, the recombination frequency declines[79,85]. Lrp binding to the low affinity site 3 inhibits recombination[86,87]. Lrp and IHF can bend the *fimS* DNA; therefore, they would allow the proper positioning of IRL and IRR that facilitates recombination[80,87]. The levels of specific amino acids will also affect Lrp binding to the *fimS* element and subsequently phase variation[86]. Lrp binding causes an orientational bias to the *fimS* element. When neither Lrp nor IHF are present at sufficient levels, H-NS will bind and maintain the Phase-OFF orientation[88]. Although Lrp binds to multiple sites within the *fimS* element, Lrp directly regulates neither *fimB* nor *fimE*.

Another protein that regulates type 1 pilus expression is the LysR-type regulator, LrhA[89]. LrhA was first identified to be associated with RpoS degradation[90]. Microarray analysis of mRNA populations from an *lrhA* mutant *vs* wild-type bacteria revealed increased expression of the *fimAICDFGH* operon. Purified LrhA protein bound to the promoter regions of both *fimB* and *fimE*; however, there was higher affinity for the *fimE* promoter. The use of *fimB*- or *fimE-lacZ* translational fusions indicated there was a greater effect with the *fimE-lacZ* fusion. Thus, LrhA appears to activate *fimE*, which would repress type 1 pilus expression.

Three other proteins have unexplained effects on type 1 pilus expression in *E. coli*: OmpX, IbeA, and IbeT. Inactivation of *ompX*, encoding an outer membrane protein OmpX, caused an increased production of FimA[91]. A disruption caused by the loss of OmpX would change the cell surface, which would affect cell-surface interactions. It is likely that OmpX acts indirectly to regulate type 1 pilus expression. A deletion of the *ibeA* gene caused diminished type 1 pilus expression, as well as lower transcription of *fimB* and *fimE*, whereas an *ibeT* mutant was shown to have the *fimS* element preferentially in the Phase-OFF orientation[92]. How each of these proteins works to regulate the *fim* genes has not been determined.

The regulatory alarmone, ppGpp, has been connected to the regulation of multiple genes in *E. coli*, including the *fim* operon. ppGpp-deficient strains exhibited diminished type 1 pili expression compared to the wild-type strain[93]. Furthermore, primer-extension analysis indicated that ppGpp activated the *fimB* P2 promoter. A follow through study demonstrated that DskA, a cofactor required for ppGpp-mediated positive regulation of several amino acid biosynthesis promoters[94], also activated transcription from the *fimB* P2 promoter[95].

Besides FimB and FimE, there are four other site-specific recombinases that could affect phase switching of the *fimS* element: HbiF, IpuA, IpuB, and IpbA. The HbiF-mediated inversion of the *fimS* element occurs primarily from Phase-OFF to Phase-ON[96]. Constitutive expression of HbiF locked the *fimS* DNA in the Phase-ON position. The three other site-specific recombinases (IpuA, IpuB, and IpbA) were discovered by sequence analysis of the UPEC strain CFT073 genome because of their high homology with the *fimB* and *fimE* genes[97]. Both IpuA and IbpA bind to the *fimS* element and mediate phase switching. IpuA functions like FimB, allowing a Phase-OFF to Phase-ON switch as well as Phase-ON to Phase-OFF switching, whereas IpbA can switch *fimS* from Phase-OFF to

Phase-ON. It is not clear under what environmental growth conditions these alternative site-specific recombinases affect the *fimS* element positioning.

Also linked to the *fimS* genetic switch are Rho and LeuX. Transcriptional termination of *fimE* was determined to be Rho-dependent, based on the use of a *rho* mutant or by treatment with bicyclomycin, an antibiotic that interferes with Rho[98,99]. Thus, when the phase switch is in the Phase-OFF position, there is a Rho-dependent termination of the *fimE* sense transcript, leading to a truncated, unstable mRNA that is readily degraded. Less FimE site-specific recombinase would allow FimB to bind and switch the *fimS* element to the Phase-ON position. The minor leucyl tRNA, LeuX, affects the *fimS* element switching from Phase-OFF to Phase-ON[100,101]. Placing the *leuX* gene on a multicopy plasmid caused greater expression from the *fimAICDFGH* operon[102].

All of the studies examining *fimB* regulation described above have concentrated on the P1 and P2 promoter regions. However, several other studies have shown that the intergenic region between the *yjhATS* operon and the *fimB* gene also plays a role in genetic regulation of *fimB*[103-105]. Sialic acid and N-acetylglucosamine inhibit the FimB recombinase. Two proteins, NagC (a N-acetylglucosamine-6P-responsive protein) and NanR (a sialic acid-responsive protein), linked to sialic acid and N-acetylglucosamine catabolism[106,107], bind to two deoxyadenosine methylation sites within the intergenic region[103-105] that align with P3 *fimB* promoter described earlier[58]. In addition, NagC also binds to an operator site 212 bp closer to the *fimB* translational start site[105]. Both proteins are thought to act as antirepressors that allow *fimB* transcription to occur[103]. However, a urinary tract infection caused by type 1 piliated UPEC will elicit an inflammatory response[108], leading to increased levels of both sialic acid and N-acetylglucosamine that will, in turn, activate some cis-active regulatory protein that shuts off *fimB* transcription.

Regulatory proteins for other pilus systems can also regulate type 1 pilus expression through a cross-talk mechanism. PapB, which affects the phase variation of the pyelonephritis associated pilus (*pap*) operon[109,110], also regulates the orientation of the *fimS* element[111-113]. In contrast to FimB, PapB inhibits the Phase-OFF to Phase-ON switching. Two proteins associated with S pili, SfaB and SfaX, also have a negative effect on Phase-OFF to Phase-ON switching[111,114]. Thus, there appears to be an expression competition between the different pilus operons. These regulatory proteins that allow expression of other types of pili in other environments counter the need for type 1 pili under growth conditions where type 1 pili are not needed.

In stationary phase-grown *E. coli* cells, type 1 pilus expression is diminished compared to logarithmic grown cells. The alternative sigma factor, RpoS, which is activated during stationary phase, represses *fimB* transcription[115]. Another regulatory signal active in a logarithmic phase culture may be provided by glucose acting as a catabolite repressor by increasing internal cAMP concentrations, which allow for greater interactions with its receptor protein, CRP[116]. For type 1 pilus expression, the role of cAMP and glucose is opaque. Early studies indicated that cAMP affected pilus expression in some strains of *E. coli*[117] and in *cya* (adenyl cyclase) mutants of *Salmonella enterica* serovar Typhimurium[118]. However, in a later study, glucose had no effect on pilus expression, even when added with exogenous cAMP or when tested in adenlyate cyclase mutants[119]. Unfortunately, some of the early work was done with the CSH50 strain of *E. coli*, which has a *fimE*::IS1 mutation[52], so the role of catabolite repression remained unclear, until recently. Using a more defined system, Müller *et al*[120] have shown that CRP-cAMP directly represses the *fimA* promoter and indirectly affects phase variation by limiting the switch from Phase-OFF to Phase-ON in a logarithmic stage population.

Two other proteins that activate *fimB* transcription are RcsB and SlyA. RcsB is part of the RcsC/RcsB two-component phosphorelay regulatory system[121]. Using an *rcsB* mutant, it was shown that under neutral pH/low osmolality growth conditions, RcsB appears to activate *fimB*[122]. Growth in an acidic environment did not affect *fimB* expression in the *rcsB* strain compared to wild-type cells. Recently, the SlyA global regulator was implicated in *fimB* gene activation[123], but the growth conditions that would favor *slyA* expression were not determined.

The last accessory protein with relevance to *fim* gene regulation is OmpR. OmpR is part of the EnvZ/OmpR two-component regulatory system that regulates genes under an osmotic stress[124]. A study by Schwan *et al*[74] found that an *ompR* mutant strain had de-repressed transcription of *fimB* and *fimE* compared to wild-type cells. More recently, they found that unphosphorylated OmpR bound to the P2 promoter of *fimB* to repress *fimB* transcription[125] (Rentchler, Lovrich, and Schwan, manuscript submitted). However, through DNase I footprinting analysis, neither unphosphorylated nor phosphorylated OmpR bound directly to the *fimE* promoter, suggesting another regulatory element that is regulated by OmpR-P would directly affect *fimE* transcription.

Thus, in addition to FimB and FimE, approximately 20 different auxiliary proteins have a role to play in the regulation of one or more *fim* genes or positioning the *fimS* element. These 20 proteins are represented in a schematic model shown in Figure 3. Some of the proteins repress *fim* gene expression (e.g. H-NS, OmpR, RpoS), whereas others appear to activate *fim* gene expression (e.g. DskA, LrhA, NagC, NanR, RcsB, SlyA). How some of these proteins may affect UPEC type 1 pilus expression during the course of a human or murine urinary tract infection is described below.

ENVIRONMENTAL SIGNALS WITHIN THE URINARY TRACT AFFECTING UPEC TYPE 1 PILUS EXPRESSION

The human or murine urinary tract is a dynamic environment. In the lower urinary tract, there are ample mannose receptors for FimH-mediated attachment of type 1 piliated UPEC cells[126]. The temperature in the urinary tract is around 37°C. Although one group showed Phase-OFF to Phase-ON switching increased at lower temperatures, others have demonstrated that the *fimA* promoter element is biased in its switch from the Phase-ON to the Phase-OFF orientation in broth cultures grown at 20°C, but the switch favors FimB recombination at 37°C[59,71,127]. More recently, Kuwahara *et al*[128] demonstrated that FimB-mediated recombination could be linked to a controlled downregulation of the Phase-ON to Phase-OFF switching rate based on a temperature-dependent suppression of the interplay of the FimE recombinase.

When the UPEC cells move from the vaginal surface, which has only a slightly acidic pH/low osmolality environment, to the urethra or ascend to the bladder, there is a switch to a moderate acidic pH/moderate to high osmolality environment[129,130]. Under the slightly acidic pH/low salt growth conditions found on the vaginal surface, proteins such as SlyA or RcsB may activate *fimB* and prevent H-NS from binding, allowing type 1 pili to be created and presented on the surface of the UPEC cells for attachment. When the bacteria move from the exterior opening of the urinary tract and ascend the urethra to the bladder, an acidic pH/moderate osmolality environment is encountered in the bladder[129,130]. A preliminary study implied that an acid tolerance system-induced protein is involved in the regulation of several *fim* genes (Schwan WR, unpublished results), which may begin to turn off the *fim* operon. Furthermore, a change in the osmolality would activate the EnvZ/OmpR two-component regulatory system, allowing OmpR to repress *fimB* transcription[74,125].

UPEC infections are ascending infections[13,131]; therefore, the presence of flagella on the UPEC cells would allow the bacteria to ascend to the kidneys. Expression of the flagella may coordinately turn off expression of the type 1 pili[132,133]. As the bacteria ascend to the kidneys, the pH would drop further and the osmolality would increase. OmpR becomes phosphorylated and activates an unknown gene whose gene product in turn potentially shuts down not only *fimB*, but also *fimE* expression. Moreover, H-NS may bind and repress both *fimB* and *fimE* at this time. This would lock the *fimS* element in the Phase-OFF position, creating nonpiliated UPEC cells. Furthermore, as the young *E. coli* population matures and moves into stationary phase, they trigger transcriptional activation of the *rpoS* gene. The acidic/high osmolality environment would cause greater translation of the *rpoS* transcripts[134], leading to more RpoS protein for repression of *fimB* transcription.

CONCLUSION

Several strains of UPEC have been shown to become nonpiliated in the murine kidney over time[13,135]. There are very few mannose receptors in human or murine kidneys[136,137] and the innate immune system is more apt to target type 1 piliated bacteria[138]; therefore, the regulatory loss of type 1 pili on UPEC cells in the human kidney would be an evolutionary advantage for these bacteria. Thus, the ability to phase vary their type 1 pilus expression offers several advantages to the UPEC. On vaginal surfaces, the outer rim of the urinary tract, and within the urethra and bladder, type 1-piliated cells benefit the bacteria because there are ample mannose receptors. When the bacteria ascend into the kidneys, the growth environment may turn off expression of an unneeded external surface structure that may target the bacteria for elimination by the host's innate defenses.

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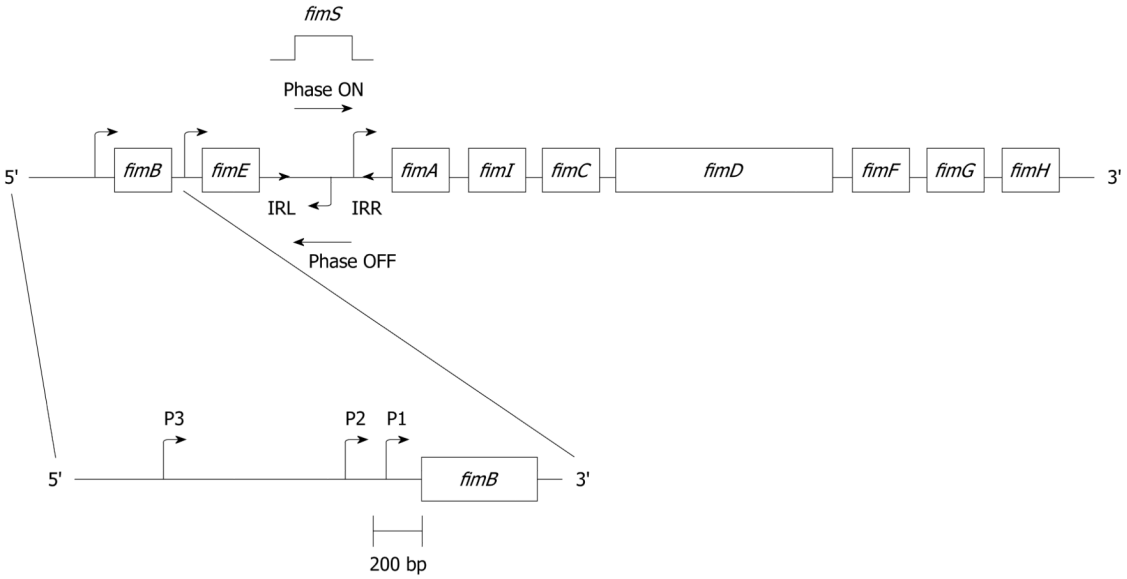

Figure 1. Schematic of the *fim* operon, including the characterized promoter sites

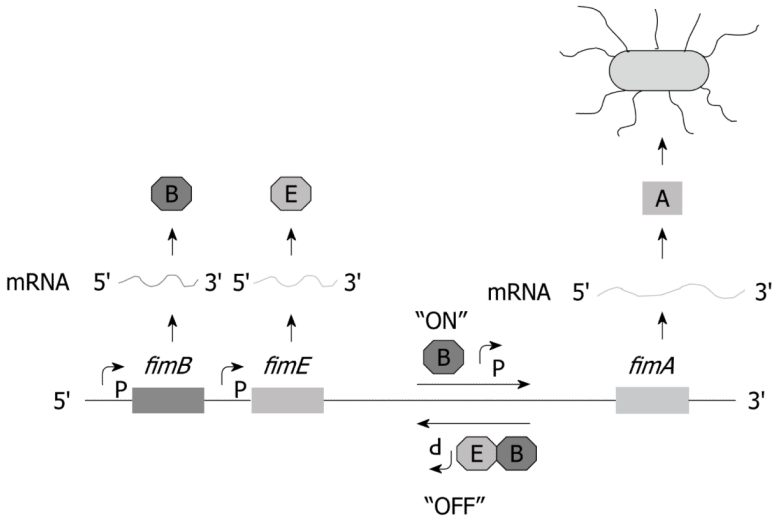

Figure 2. A schematic showing how the FimB and FimE proteins orient the *fimS* element

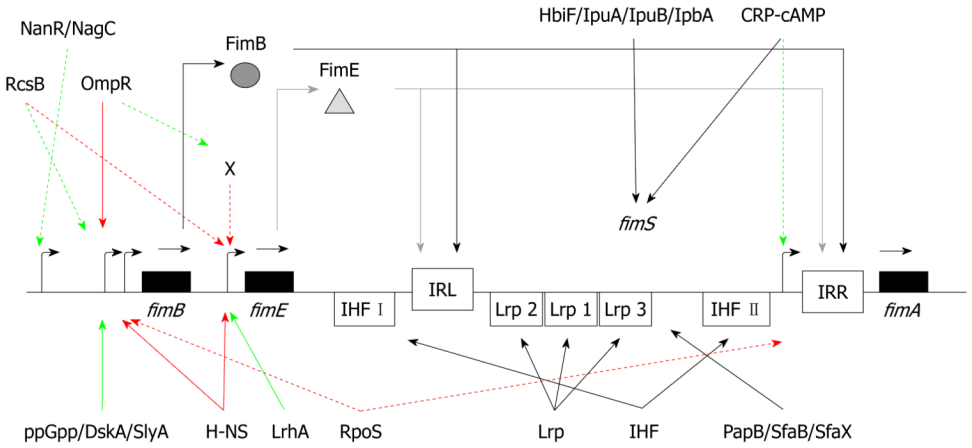

Figure 3. Schematic model of the actions of 20 auxiliary proteins on the regulation of type 1 pili

The inverted repeat left and right (IRL and IRR) are shown as open boxes. Binding sites for integration host factor (IHF I and II) and leucine-responsive protein (Lrp1, 2, and 3) are also represented as open boxes. Genes are displayed as black boxes and the promoters are shown as bent black arrows. The dark gray arrows correspond to FimB and the light gray arrows are for FimE. Black arrows signify an effect on the *fimS* element. Solid green arrows indicate confirmed binding associated with stimulatory effects, whereas dashed green arrows indicate presumed stimulatory effects. Solid red arrows indicate confirmed binding associated with repressing effects, whereas dashed red arrows indicate presumed repressing effects.