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MicroReview

FtsK, a literate chromosome segregation machine

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Summary

The study of chromosome segregation in bacteria has gained strong insights from the use of cytology techniques. A global view of chromosome choreography during the cell cycle is emerging, highlighting as a next challenge the description of the molecular mechanisms and factors involved. Here, we review one of such factor, the FtsK DNA translocase. FtsK couples segregation of the chromosome terminus, the *ter* region, with cell division. It is a powerful and fast translocase that reads chromosome polarity to find the end, thereby sorting sister *ter* regions on either side of the division septum, and activating the last steps of segregation. Recent data have revealed the structure of the FtsK motor, how translocation is oriented by specific DNA motifs, termed KOPS, and suggests novel mechanisms for translocation and sensing chromosome polarity.

Introduction

Active DNA transport plays key roles in orchestrating the dynamics of bacterial genomes. Its involvement in acquisition of foreign genes during conjugation and in segregation of chromosomes during spore formation and cell division has a direct influence on genetic diversity and genome stability. The FtsK/SpoIIIE/Tra family of DNA

translocases is implicated in these three activities. Tra proteins, encoded by conjugative elements, act during conjugation (e.g. the TraSA protein from the Streptomyces mobile element pSAM2) (Kendall and Cohen, 1987; Kataoka *et al.*, 1991; Smokvina *et al.*, 1991), SpoIIIE is required for complete transfer of the chromosome into the developing spores of sporulating bacteria (e.g. *Bacillus subtilis*) (Wu and Errington, 1994), and FtsK is required for both cell division and faithful segregation of sister chromosomes during vegetative cell division (Lesterlin *et al.*, 2004). This family of translocases act on double-stranded DNA (dsDNA) and are highly conserved throughout eubacteria (with exceptions to cyanobacteria) (Bath *et al.*, 2000; Possoz *et al.*, 2001; Aussel *et al.*, 2002). A homologue of FtsK, HerA, is found in archaea, establishing an FtsK/HerA superfamily of ATP-driven DNA pumps for all prokaryotes (Iyer *et al.*, 2004; Hanson and Whiteheart, 2005). A DNA tracking activity has been demonstrated *in vitro* for SpoIIIE (Bath *et al.*, 2000) and FtsK (Aussel *et al.*, 2002) and 'single-molecule' experiments have shown that FtsK is a powerful translocation motor that mobilizes DNA against high forces at extreme high speed (Saleh *et al.*, 2004; Pease *et al.*, 2005).

Data emerging from *in vivo* and *in vitro* studies, mainly performed in *Escherichia coli*, together with the crystal structure of FtsK from *Pseudomonas aeruginosa* have provided significant insights into the mechanism of translocation and how it is controlled *in vivo*. This review focuses on these recent advances.

The FtsK family of DNA translocases

FtsK is a multifunctional and multidomain protein. The N-terminal domain (FtsK_N) serves to localize the protein to the division septum and is required for cell division (Begg *et al.*, 1995; Draper *et al.*, 1998; Yu *et al.*, 1998a) while the C-terminal domain (FtsK_C) forms the translocation motor involved in chromosome segregation. The general structure and sequence conservation of FtsK is shown in Fig. 1. FtsK_N is ~200 residues long and poorly conserved at the sequence level. It, however, invariably contains transmembrane helices that tether the protein to the cell membrane specifically at the division septum (Fig. 1) (Dorazi and Dewar, 2000), where it is proposed to interact

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Pseudomonas aeruginosa FtsK

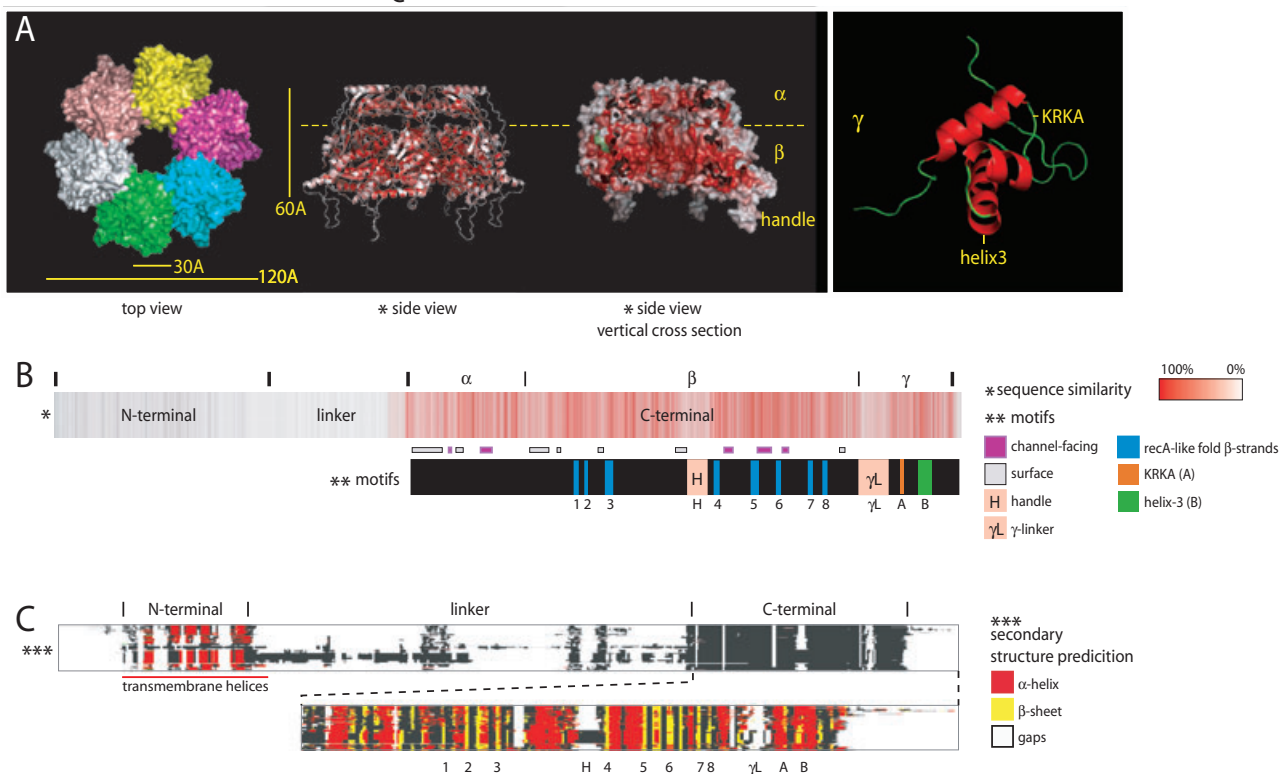


Fig. 1. *Pseudomonas aeruginosa* FtsK domain organization and conservation.

A. Images of the crystal structure of hexameric FtsK from *P. aeruginosa* (α and β domains) (Massey *et al.*, 2006) and of the NMR structure of the γ domain (Sivanathan *et al.*, 2006). The top view shows the six subunits (in unique colours) that form the hexamer. The side views and (B) are colour-coded according to sequence similarity when comparing FtsK across eubacteria with deeper red indicating higher conservation [obtained using ProtSkin (<http://www.mcg.nmr.ca/ProtSkin>)]. It clearly illustrates the cleft between the α and β domains and the conservation of residues lining the central channel (cross-section). The KRKA loop that interacts with XerD and helix-3 that is involved with KOPS recognition are indicated within the γ subdomain.

B. A schematic of the general domain organization of FtsK using STRAP (<http://www.charite.de/bioinf/strap>) superimposed on annotated motifs for *P. aeruginosa*'s FtsK. Motifs within the C-terminal domain highlight the regions of high- and low-sequence conservation; the residues lining the central channel (upon hexamerization), the RecA fold β -strands and the regulatory domains within γ (motifs A and B) are among the highest conserved regions, while the residues on the outer surface of the hexamer, the handle and the γ -linker vary considerably.

C. A schematic of an FtsK sequence alignment (Deprez *et al.*, 2005) with secondary structure prediction using. FtsK homologue was selected from a BLAST in all sequenced bacterial genomes with a cut-off at $1.e^{-100}$. The three main domains are annotated for *P. aeruginosa* FtsK. Gaps litter the linker domains (linker and γ L), highlighting their variable length. The transmembrane helices of the N-terminal and the α -helices and β -strands of the C-terminal are strongly conserved. The handle region (H) within the C-terminal domain is prevalent only in proteobacteria. Predicted coiled coil structures in the linker domain are restricted to the long linkers and are thus not shown.

with several other cell division proteins (Di Lallo *et al.*, 2003). Unlike FtsK_C which forms multimers (see below), the tertiary structure formed by FtsK_N is unknown, rendering a general model for the structure of septum-borne FtsK difficult to draw. An attractive hypothesis is that FtsK_N requires other division proteins and/or the process of septum closure itself to oligomerize, which may restrict the formation of active FtsK_C multimers to a certain stage of septum closure, thus controlling FtsK activity temporally. The linker domain (FtsK_L) separates FtsK_N from FtsK_C and extends into the cytoplasm from the division septum. It shows high sequence and length variability. The longest linkers (~600 aa) are found in proteobacteria, and, in *E. coli*, it is required for proper

function of FtsK_C activities (Bigot *et al.*, 2004). The longer linkers tend to be rich in proline and glutamine residues, and many adopt coiled coils as predicted secondary structures, suggesting they might participate in the formation of FtsK multimers and/or in interaction with other divisome proteins (not shown; see legend of Fig. 1).

FtsK_C, the signature domain of this protein, can be further subdivided into α , β and γ subdomains (Yates *et al.*, 2003). The α and β subdomains form the DNA pump (Massey *et al.*, 2006) while the γ subdomain controls translocation by recognition of KOPS (see below) motifs in the DNA and interacts with and controls other proteins involved in segregation (i.e. the Xer recombination machine, see below and Yates *et al.*, 2006). The

recently solved crystal structure of *P. aeruginosa*'s FtsK (consisting of only the α and β subdomains) revealed that six FtsK_C domains oligomerize to form a ring that can accommodate dsDNA (Massey *et al.*, 2006). The α subdomains form a smaller ring atop a larger β ring (Fig. 1). Note that the crystallized FtsK is truncated of FtsK_N, FtsK_L and of the γ subdomain, and was solved as double head-to-head hexamers that interact via a 'handle' domain (Fig. 1A). However, a double hexamer is difficult to reconcile with functional data, in particular because γ , which is almost directly linked to β , must contact the DNA and thus be positioned in the vicinity of the central channel. Consistent with this view, the handle domain is not conserved (Fig. 1B and C). The β subdomain contains the core RecA-like fold (with Walker P-loop and B motifs) that is common to AAA⁺ proteins (ATPases Associated with various cellular Activities), and generates the force required for DNA translocation. It is both the conservation of several sequence motifs and distinct β -strand order and structural arrangement within the RecA-like domain (distinct from other P-loop ATPases), as well as the ability to translocate dsDNA that defines the FtsK/SpoIIIE/Tra family of DNA translocases (Fig. 1).

FtsK is the fastest known DNA pump, with translocation rates of up to 7 kb s⁻¹ (Saleh *et al.*, 1996; Pease *et al.*, 2005). Contrary to previously described translocases (i.e. Eco124i; Stanley *et al.*, 2006), FtsK does not rotate to track the grooves of dsDNA during translocation, but rather rotates only once per 150 bp translocated (Saleh *et al.*, 2005). Comparing structures of ATP γ S-bound FtsK (in a hexamer) and ADP-bound FtsK monomers suggests a conformational change between the α and β subdomains upon ATP hydrolysis that would correspond to a 1.6 bp displacement of DNA (Massey *et al.*, 2006). This displacement would position the DNA helix to contact the same position on the following subunit of the hexamer with only moderate rotation required. Based on these observations, Massey *et al.* (2006) have proposed a 'rotary inchworm' model for translocation in which each subunit of the translocase would hydrolyse ATP sequentially around the hexamer (see also Strick and Quessada-Vial, 2006).

At the tail end of FtsK_C, the γ subdomain forms a winged helix–turn–helix (wHTH) that is attached to the β domain via a flexible linker. wHTH folds are commonly associated with DNA binding, while some participate in protein–protein interactions (Gajiwala and Burley, 2000). The γ domain utilizes both functions and acts as a regulatory domain, with loop1 forming an epitope that interacts with the recombinase XerD and helix3 recognizing specific DNA motifs, the KOPS (see below) (Ptacin *et al.*, 2006; Sivanathan *et al.*, 2006; Yates *et al.*, 2006).

There are instances of two to three conserved FtsK motor domains ($\alpha\beta$ domains) occurring within a single ORF (identified from whole genome sequencing). Such arrangement might promote the formation of active motors. Several of these ORF also encode further specialized domains, suggesting that the FtsK motor domains may provide the translocation activity required to assist different processes. Striking examples include FtsK motor domain(s) fused to a phage integrase or a forkhead-associated domain (ORFS SC6A9.34 and CtheDRAFT_1197 from *Streptomyces coelicolor* and *Clostridium thermocellum* respectively).

FtsK is part of the divisome

The co-ordinated action of about 15 proteins is necessary for *E. coli* cell division (for review see Goehring and Beckwith, 2005; Vicente *et al.*, 2006). These proteins localize at midcell and assemble into a multiprotein complex termed the septal ring or divisome. Septation then occurs by constriction of the divisome-associated membranes. FtsK is part of the divisome and studies with truncated forms revealed that only FtsK_N is essential for septum formation in *E. coli*; its absence provokes the formation of long cell filaments with no septum constriction (Draper *et al.*, 1998; Wang and Lutkenhaus, 1998).

FtsK is among the first divisome proteins to localize at midcell and its localization is required for the recruitment of other divisome components (Wang and Lutkenhaus, 1998; Yu *et al.*, 1998a; Chen and Beckwith, 2001). Overexpression of some divisome proteins (FtsQ, FtsN or co-overproduction of FtsZ and FtsQ together with a mutant form of FtsA) partially suppresses the lethality due to a deletion of FtsK, suggesting that it primarily serves to stabilize the divisome prior to septation (Draper *et al.*, 1998; Geissler and Margolin, 2005; Goehring *et al.*, 2006). The added fact that neither of the two FtsK homologues in *B. subtilis* (SpoIIIE and YtpT) is essential (Sharpe and Errington, 1995) further suggests that FtsK does not play a conserved active role during divisome assembly. Nevertheless, overexpression of other cell division proteins in *ftsK*-deleted cells is not sufficient for normal division in *E. coli*; suppressed strains still exhibit cell chains (filaments with deep septum constrictions) indicative of a defect in septum closure (Draper *et al.*, 1998; Geissler and Margolin, 2005). SpoIIIE has been proposed to play a role in the late stages of membrane fusion during spore formation in *B. subtilis* (Sharp and Pogliano, 2003; Liu *et al.*, 2006). FtsK may play an analogous role in *E. coli*. Although poorly understood, the observations that FtsK interacts genetically with DacA and may interact physically with FtsI, both involved in peptidoglycan synthesis,

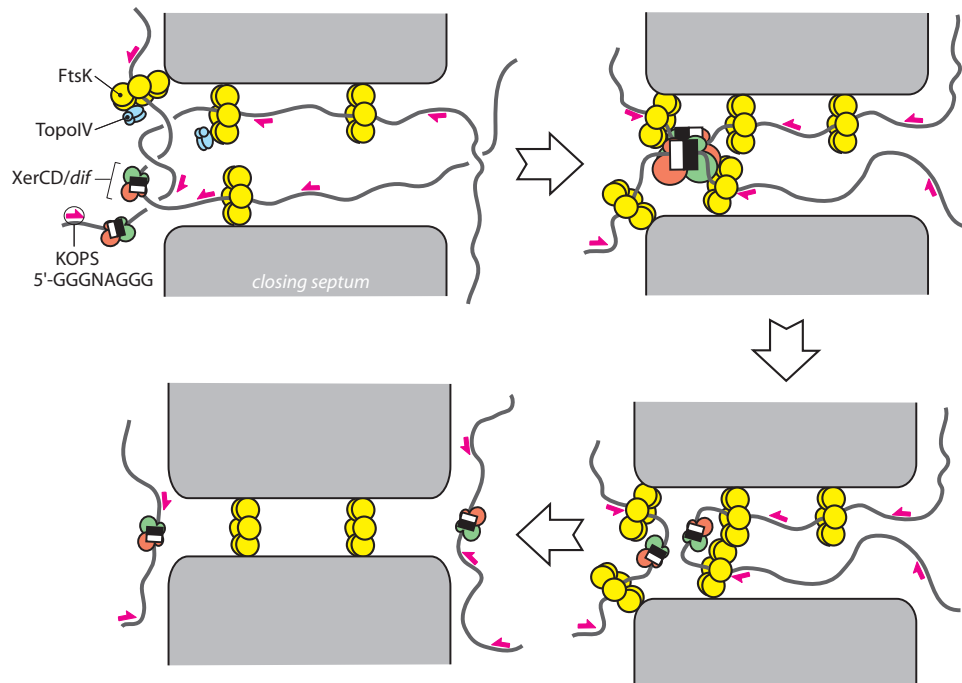


Fig. 2. Segregation of the *ter* region during chromosome dimer resolution. The drawing represents the central part of a dividing cell. The closing division septum, septum-associated FtsK hexamers, Topo IV, the XerCD/*dif* complex and some KOPS are indicated. Only FtsK_C is represented as hexamers. FtsK_N's and FtsK_L's roles are symbolized by an interaction of FtsK_C with the septum membrane. Top left: sister chromosomes are dimeric and intercatenated and chromosomal DNA is stretched across the septum. FtsK binds to this DNA in an oriented manner by recognizing KOPS and translocates towards XerCD/*dif* complexes. This process sorts the *ter* region of sister chromosome to either side of the septum and helps decatenation by Topo IV. Top right: FtsK reaches the XerCD/*dif* complexes and contacts XerD to induce recombination. Bottom right: the dimer is resolved and FtsK finishes sorting sister chromosomes, allowing septum closure without chromosome damage (bottom left).

may be relevant to this role (Begg *et al.*, 1995; Draper *et al.*, 1998; Di Lallo *et al.*, 2003).

While not essential for growth, deletion of all or part of FtsK_L and of FtsK_C also interferes with septum formation as judged by the appearance of cell filaments and cell chains (Yu *et al.*, 1998b; Recchia *et al.*, 1999; Bigot *et al.*, 2004). These defects cannot be entirely explained by the inactivation of chromosome dimer resolution, indicating that FtsK_C and FtsK_L both play a role in cell division (Bigot *et al.*, 2004).

The early divisome components, including FtsK, are often observed localized at midcell of cells without constricted septa (Wang and Lutkenhaus, 1998). This delay between localization of early divisome proteins and septum constriction does not reflect the time required to assemble late divisome proteins. Indeed, all proteins recruited after FtsK assemble simultaneously at the time of septation (Aarsman *et al.*, 2005). This leaves a broad window for action by FtsK towards the end of the cell cycle (Wang *et al.*, 2005). However, chromosome dimer resolution seems to occur late in the cell cycle, concomitantly with septum constriction (Steiner and Kuempel, 1998a). This raises the question of the state of FtsK from its recruitment to midcell to activation of dimer resolution,

and may indicate that FtsK activity is controlled by the late completion of divisome assembly or even by septum constriction.

FtsK sorts sister chromosomes

Segregation of bacterial chromosomes involves multiple processes acting at different stages of the cell cycle on specific chromosome regions (for reviews see Sherratt, 2003; Gitai *et al.*, 2005; Espeli and Boccard, 2006). In *E. coli*, FtsK acts in the region where replication terminates (*ter*) at the last stage of chromosome segregation, which is concomitant with constriction of the division septum (Steiner and Kuempel, 1998a; Steiner *et al.*, 1999). At this stage, two kinds of physical links, intercatenation links and chromosome dimers, may persist between sister chromosomes. FtsK controls the removal of these links and couples it with cell division (Fig. 2).

Intercatenation links are resolved by topoisomerase IV (Topo IV), a type II topoisomerase composed of two subunits, ParC and ParE (Adams *et al.*, 1992; Peng and Marians, 1993). The activity of Topo IV is temporally and spatially regulated (Espeli *et al.*, 2003a,b). Active Topo IV is formed preferentially during the last stages of the cell

cycle, from termination of replication to cell division. The ParC subunits appear colocalized with the replication machinery. However, it also interacts with FtsK_C, stimulating Topo IV activity *in vitro*. In contrast, the ParE subunits appear distributed in the DNA-free space of the cell. K. Mariani and co-workers (Espeli *et al.*, 2003a) have suggested that FtsK acts to capture ParC after disassembly of the replisome. Free ParE could then associate with the ParC–FtsK complex to reconstitute active Topo IV. This ensures the spatial and temporal regulation of decatenation activity. However, the fact that Topo IV is essential whereas FtsK_C is not strongly suggests that decatenation by Topo IV can occur in the absence of FtsK.

In addition to catenation links, the sister chromosome may be dimeric (reviewed in Lesterlin *et al.*, 2004; Fig. 2). In *E. coli*, chromosome dimers form by homologous recombination between sister chromosomes during replication. This occurs in about 15% of the cells during growth in standard laboratory conditions (Steiner and Kuempel, 1998b; Perals *et al.*, 2000). The dedicated safeguard system, XerCD/*dif*, consists of two tyrosine recombinases, XerC and XerD, which act at a specific site located in *ter*, *dif*. Dimer resolution depends on FtsK_C, which plays at least two distinct role in this process (Fig. 2) (Capioux *et al.*, 2002; Yates *et al.*, 2003; Bigot *et al.*, 2004). FtsK loads onto DNA stretches in the vicinity of the closing septum and translocates DNA towards the duplicated *dif* sites. This sorts sister chromosomes on either side of the septum and may aid decatenation by Topo IV. Chromosome mobilization finally allows the formation of a productive recombination synapse between XerCD/*dif* complexes. This may involved either bringing the two XerCD/*dif* complexes together in a productive conformation or remodelling a pre-existing synapse to an active conformation. Recombination is then activated by a direct interaction between FtsK_C and XerD, which activates XerD catalytic activity (Massey *et al.*, 2004; Yates *et al.*, 2006). This interaction is mediated by the extreme C-terminal subdomain of FtsK, FtsK_γ (Fig. 1) (Yates *et al.*, 2006). The FtsK–XerCD/*dif* system may also be directly involved in chromosome decatenation as successive rounds of recombination can remove catenation links *in vitro* (Ip *et al.*, 2003). XerCD/*dif* may also control Topo IV activity as a preferential region for Topo IV action exists in the immediate vicinity of *dif* (Hojgaard *et al.*, 1999). Surprisingly, this activity depends on XerC and XerD but not on FtsK_C. It is thus conceivable that XerCD and Topo IV are parts of a multiprotein complex acting to separate sister *ter* regions, the formation of which does not strictly depend on FtsK.

FtsK reads the polarity of the chromosome

A key implication of the general model presented in Fig. 2 is that FtsK has to find its way to the *dif* site. *In*

in vivo data indicate that the loci entrapped in the septum in the case of a dimer are included in a restricted but rather long part of the chromosome, up to 400 kb around *dif*, called the FtsK domain (Corre and Louarn, 2005; C. Pages and F. Cornet, in preparation). These data strongly suggest two levels of active positioning of the *ter* region. The first is global positioning of a large terminal domain close to the septum. This does not require FtsK and is independent of dimer formation. The second involves precise positioning of the XerCD/*dif* complexes by translocating FtsK. FtsK thus loads onto DNA several kilo base pairs away from the *dif* site and must translocate towards *dif* to avoid unproductive activity. While it has been known for a long time that dimer resolution requires the correct orientation of the sequences flanking *dif* (Cornet *et al.*, 1996; Kuempel *et al.*, 1996; Corre *et al.*, 2000; Perals *et al.*, 2000), the demonstration that this orientation controls FtsK translocation and the identification of the DNA motifs involved are recent discoveries (Corre and Louarn, 2002; Bigot *et al.*, 2005; Levy *et al.*, 2005; Pease *et al.*, 2005). FtsK recognizes short DNA motifs, termed KOPS (FtsK Orienting Polar Sequences), 5'-GGGNAGGG-3', which are over-represented on the chromosome and strongly biased for their orientation towards *dif*. This biased distribution of KOPS is conserved in bacteria closely related to *E. coli* and analyses of other bacterial genomes generally reveal other motifs with KOPS-like distribution, suggesting that the control of FtsK by KOPS is conserved in bacteria (Eisen *et al.*, 2000; Levy *et al.*, 2005; Hendrickson and Lawrence, 2006). Indeed, this is reminiscent of the other skewed sequence whose role has been described thus far, the Chi motif. Chi are recognized by RecBCD complexes translocating from a dsDNA end and switch RecBCD activity from DNA degradation to the creation of RecA-associated single stranded loops that are used for strand exchange during homologous recombination (Taylor *et al.*, 1985; Dixon and Kowalczykowski, 1993; Dohoney and Gelles, 2001; Spies *et al.*, 2003). Motifs unrelated to the *E. coli* Chi motif but with Chi activity have been reported in other bacteria (El Karoui *et al.*, 1998; Sourice *et al.*, 1998; El Karoui *et al.*, 1999). The control of DNA trafficking by short motifs with biased distribution thus appears as a general feature in bacteria. Both KOPS and Chi skews contribute to the global replicore orientation, which accounts for a general organization of bacterial chromosomes following the replication origin to *dif* axis and now appears as a major player in chromosome structure and dynamics.

Although FtsK may load on any piece of dsDNA tested so far, KOPS are preferred sites of loading and are thought to orient translocation at this step (Fig. 3) (Bigot *et al.*, 2006). KOPS also block and eventually reverse the direction of translocation when encountered from

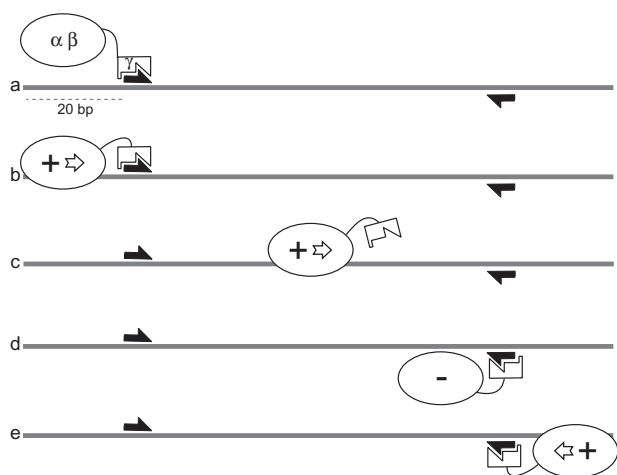


Fig. 3. Model for KOPS-directed FtsK loading and translocation reversal. For clarity, only one FtsK monomer is represented with the $\alpha\beta$ motor and the γ subdomains indicated. FtsK_N and FtsK_L are omitted. The status of the FtsK translocation motor is indicated (+: active; -: inactive). The grey line is a DNA duplex with KOPS indicated by the arrows. (a) FtsK loads onto the DNA by recognizing a KOPS and forms an active hexamer (b). This requires at least 20 bp of DNA upstream the KOPS (Bigot *et al.*, 2006). (c) Upon recognition of a non-permissive KOPS, FtsK stops and the hexamer eventually disassembles (d). (e) The same or another motor then reassembles in the permissive orientation.

their 3' end (Fig. 3) (Bigot *et al.*, 2005; Levy *et al.*, 2005). This blockage is not total in *in vivo* and *in vitro* assays, strongly suggesting that KOPS recognition by FtsK is stochastic (Bigot *et al.*, 2005). Indeed, it is estimated that FtsK_{50C}, the truncated version of FtsK used *in vitro*, stops only in 60% of the case when it encounters a single KOPS from its 3' end. This probability may be close to optimal for FtsK to rapidly locate *dif*, giving that the orientation bias of the KOPS on the chromosome is not total (Levy *et al.*, 2005). KOPS are recognized by the winged-helix γ subdomain (Ptacin *et al.*, 2006; Sivanathan *et al.*, 2006). Notably, this subdomain also contains the KRKA motif that interacts with XerD and is connected to the $\alpha\beta$ motor by a flexible linker (Fig. 1). γ may thus binds KOPS-containing DNA to orient loading of the $\alpha\beta$ motor. Translocating with γ at the front end of the motor then positions this subdomain to interact with KOPS or a XerD-bound *dif* site.

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