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MicroReview

Linear plasmids and chromosomes in bacteria

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Summary

Linear plasmids and chromosomes were unknown in prokaryotes until recently but have now been found in spirochaetes, Gram-positive bacteria, and Gram-negative bacteria. Two structural types of bacterial linear DNA have been characterized. Linear plasmids of the spirochaete *Borrelia* have a covalently closed hairpin loop at each end and linear plasmids of the Gram-positive filamentous *Streptomyces* have a covalently attached protein at each end. Replicons with similar structures are more frequent in eukaryotic cells than in prokaryotes. Linear genomic structures are probably more common in bacteria than previously recognized, however, and some replicons may interconvert between circular and linear isomers. The molecular biology of these widely dispersed elements provides clues to explain the origin of linear DNA in bacteria, including evidence for genetic exchange between prokaryotes and eukaryotes.

Introduction

The bacterial genome has long been considered to consist solely of circular DNA molecules. According to this paradigm, a eukaryotic cell contains separate linear chromosomes, but a prokaryotic cell contains a unique, haploid, circular chromosome and often one or more circular plasmids. This picture emerged from pioneering studies of the *Escherichia coli* chromosome and was reinforced by finding circular plasmids and chromosomes in other bacteria. Mitochondria and chloroplasts, which share a common ancestry with prokaryotes, also were found in general to contain circular genomes.

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This classical view must now be amended in view of a new round of examinations of the bacterial genome. Pulsed-field gel electrophoresis, used to separate large DNA molecules and to distinguish between circular and linear forms, has revealed that prokaryotes show a variety of genomic configurations. In 1989, the first linear bacterial chromosome was discovered in the arthropod-borne spirochaete *Borrelia burgdorferi*, the agent of Lyme disease (Baril *et al.*, 1989; Ferdows and Barbour, 1989). Linear chromosomes have since been reported for *Streptomyces coelicolor*, *Streptomyces lividans* (Chen *et al.*, 1993a) and *Rhodococcus fascians* (Crespi *et al.*, 1992), which are members of the high G+C subdivision of Gram-positive bacteria. A multipartite genome consisting of one linear and one circular chromosome has been reported for *Agrobacterium tumefaciens* (A. Allardet-Servent, personal communication), a Gram-negative member of the α-group Protobacteriaceae. Other bacteria in this group have two distinct circular chromosomes, or one chromosome and one or more megaplasmids (Michaux *et al.*, 1993; Suwanto and Kaplan, 1989).

Bacterial linear plasmids were first described in *Streptomyces rochei* in 1979 (Hayakawa *et al.*, 1979) and have now been detected in at least 10 other *Streptomyces* spp. as well as in the related bacteria *R. fascians* (Crespi *et al.*, 1992) and *Nocardia opaca* (Kalkus *et al.*, 1990). Linear plasmids are found in all members of the genus *Borrelia* (Plasterk *et al.*, 1985; Marconi *et al.*, 1993). A linear plasmid has also been reported in the Gram-negative *Thiobacillus versutus* (Wlodarczyk and Nowicka, 1988) and the prophage of coliphage N15 is a linear plasmid (Svarchevsky and Rybchin, 1984).

The discovery of linear chromosomes and plasmids in bacteria raises several questions. What are their molecular structures and replication mechanisms and how do they compare with more familiar linear DNA models? Also, since circular DNA typifies most prokaryotes, how did linear DNA originate in certain bacteria and what is its biological significance?

Prokaryotic telomeres

In characterizing a linear genome, it is reasonable to begin at its ends. In fact, proof of a linear genomic structure requires demonstrating unique molecular ends. A

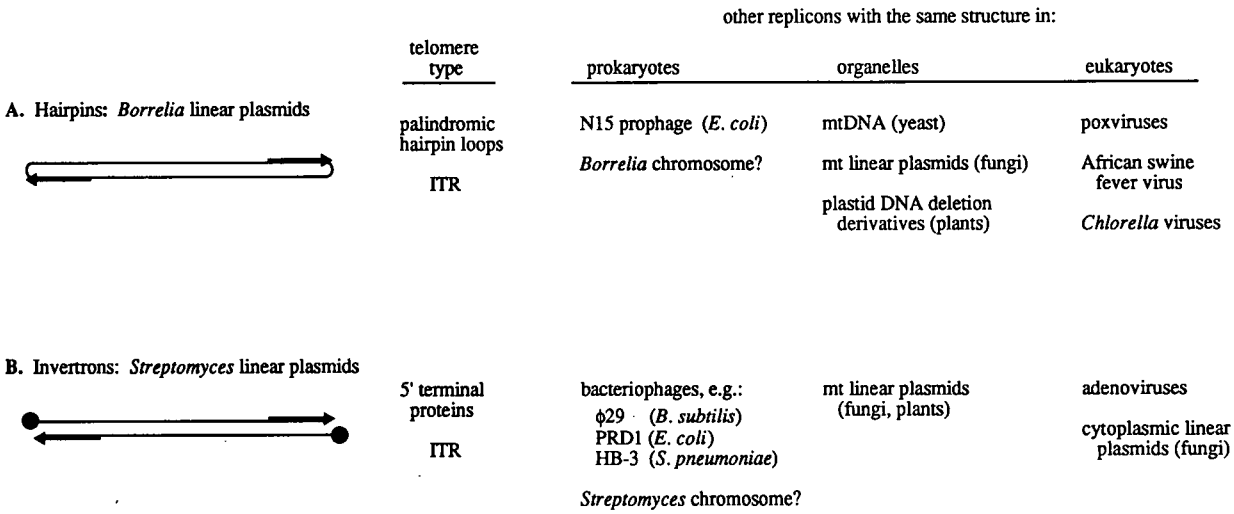

Fig. 1. Molecular structure of bacterial linear plasmids. ITR, inverted terminal repeat (indicated by arrows); mt, mitochondrial.

telomere is the region of DNA at the end of a linear replicon that is essential for the stability and complete replication of the molecule (Blackburn, 1991). One type of telomere, found on eukaryotic chromosomes from protozoa to humans, is composed of tandemly repeated, simple sequences (Blackburn, 1991). The prokaryotic linear replicons that have been characterized exhibit two very different telomere types, reflecting different strategies for stabilizing and replicating the ends (Fig. 1).

Borrelia *linear plasmids: hairpin telomeres*

Spirochaetes of the genus *Borrelia* have a predominantly linear genomic structure. All species that have been examined contain a 950–1000 kb linear chromosome and several linear plasmids that range in size from 5 kb to greater than 200 kb (Baril *et al.*, 1989; Ferdows and Barbour, 1989; Stålhammar-Carlemalm *et al.*, 1990; M. S. Ferdows and A. G. Barbour, personal communication). Borrelias also contain circular plasmids, the prototypical form of bacterial plasmid. The physical map of the *B. burgdorferi* chromosome is linear (Casjens and Huang, 1993; Davidson *et al.*, 1992), but the chromosomal telomeres have not yet been isolated and analysed.

The structure of a 16 kb linear plasmid of *B. burgdorferi* has been characterized in the most detail (Hinnebusch and Barbour, 1991; Hinnebusch *et al.*, 1990). At each end of this plasmid, the two DNA strands are connected and form a perfectly palindromic AT-rich terminal hairpin loop. A conserved 19 bp inverted repeat sequence is present at each end of the plasmid, comprising an inverted terminal repeat. All *Borrelia* linear plasmids analysed to date appear to have these telomeric features (Barbour and Garon, 1987; Kitten and Barbour, 1990).

The prophage of the unusual temperate coliphage N15 is similar in structure to *Borrelia* linear plasmids (Svarchevsky and Rybchin, 1984). N15, like λ, has a double-stranded linear DNA genome with cohesive ends. Its prophage, however, replicates extrachromosomally in *E. coli* as a 46 kb linear plasmid. The N15 prophage has palindromic terminal hairpin loops and a 28 bp inverted terminal repeat (Malinin *et al.*, 1992b).

All other examples of this telomeric structure are found in eukaryotic cells and their viruses. *Borrelia* linear plasmids most closely resemble the genomes of vaccinia and other animal poxviruses (Baroudy *et al.*, 1982), African swine fever virus (ASFV) (González *et al.*, 1986), and mitochondria of the yeast *Pichia* (Dinouël *et al.*, 1993). These genomes also have AT-rich single-stranded hairpin loops that covalently link the two DNA strands, and inverted terminal repeats. The mitochondrial DNA of *Paramecium* has an AT-rich hairpin loop at one end (Pritchard and Cummings, 1981).

Some other eukaryotic linear genomes have hairpin structures, but the nucleotide sequences of their terminal single-stranded loops have not been determined. This group includes viruses of the unicellular alga *Chlorella* (Rohozinski *et al.*, 1989), mitochondrial plasmids of the plant pathogenic fungus *Rhizoctonia solani* (Miyashita *et al.*, 1990), and deletion derivatives of the chloroplast genome of rice (Harada *et al.*, 1992).

Streptomyces *linear plasmids: invertron telomeres*

A different type of linear plasmid is found in several species of the filamentous soil bacteria *Streptomyces.* These plasmids, which range from 9 kb to more than 600 kb, have a terminal protein covalently attached to the

5' end of each DNA strand, as well as inverted terminal repeats (Sakaguchi, 1990). The *Streptomyces* chromosome may have a similar structure (Chen *et al.*, 1993a; C. Chen and H. Kieser, personal communication). These telomeric features place the *Streptomyces* plasmids in a widely dispersed class of linear DNA replicons encountered mainly in eukaryotic cells (Fig. 1). Virtually every eukaryotic linear plasmid is of this type, including cytoplasmic, mitochondrial, and chloroplast plasmids of many fungi, algae, and higher plants (Meinhardt *et al.*, 1990). Adenoviruses, which infect animal cells, also have genomes with this type of telomere (Horwitz, 1990). Among prokaryotes, a few phages, including the *Bacillus subtilis* phage φ29, *Streptococcus pneumoniae* phage HB-3, and *E. coli* phage PRD1 have the same structure as the *Streptomyces* linear plasmids (Salas, 1988).

Several other features link these phylogenetically diverse elements. Although they have not yet been characterized for *Streptomyces* linear plasmids, the DNA polymerases utilized by other members of this group are more closely related to eukaryotic DNA polymerase α than to prokaryotic DNA polymerase PolI (Salas, 1991). Many, including bacteriophage HB-3 (Romero *et al.*, 1990), several fungal and plant mitochondrial plasmids (Meinhardt *et al.*, 1990), Adenovirus (Horwitz, 1990), and linear plasmid SCP1 of *Streptomyces* (Kinashi *et al.*, 1992) can integrate into the host chromosome. Sakaguchi (1990) proposed the term invertron for these autonomously replicating mobile genetic elements with covalently attached terminal proteins and inverted terminal repeats, and discussed their structural and functional similarities to transposons.

Replication of bacterial linear DNA

As first pointed out by Watson (1972), it is not obvious how the ends of a linear molecule can be completely replicated. Every DNA polymerase requires a pre-existing primer, usually a short RNA molecule, to provide a free 3'-OH group for initiating 5'-to-3'-directed growth. Once a linear molecule is primed at one end, the nascent strand can grow to the opposite end. However, primer removal leaves the daughter molecule with a 3' tail of unreplicated DNA. This dilemma is resolved by replication mechanisms that rely on special features of the telomeres.

Hairpin plasmid replication

When the rules of enzymatic DNA polymerization became known, Cavalier-Smith (1974) and Bateman (1975) theorized that telomeres were palindromic hairpins and showed how these structures could provide a means of complete replication. Their models, originally proposed for eukaryotic chromosomes, precisely describe the telomeres of *Borrelia* plasmids. The Bateman Model predicts a concatemeric replicative intermediate, in which unit-length genomes are connected by duplex forms of the hairpin loop sequence. We have found evidence for such a concatemer junction, composed of the fused left and right ends of the *Borrelia* 16 kb linear plasmid (K. Tilly and J. Fuhrman, unpublished; J. Hinnebusch and A. G. Barbour, unpublished). Whether this junction fragment was derived from a replicative form of the *Borrelia* linear plasmid is not known, but similar concatemer junctions are present in replicative forms of vaccinia virus (Merchlinsky and Moss, 1986). A duplex form of the N15 prophage hairpin sequences also occurs in the middle of the encapsidated phage genome (Malinin *et al.*, 1992a).

Although no replication origins have been identified for the *Borrelia* plasmids or chromosome, preliminary genetic mapping of its linear chromosome suggests two possible locations. The DNA replication genes *dnaA*, *dnaN*, *gyrB*, and *gidA* are near the chromosomal origins of other bacteria. In *B. burgdorferi*, the *dnaA* cluster is at the centre of the chromosome but the *gidA* gene is near the left end. Old *et al.* (1992) proposed that the replication origin is at one of these locations.

Invertron replication

Streptomyces linear plasmids and other invertrons probably replicate by the protein-primed DNA replication mechanism that has been well characterized for *B. subtilis* phage φ29 and Adenovirus (Salas, 1991). The telomere is the origin of replication and is recognized by specific initiation proteins that promote unwinding. The 5'-terminal protein (TP) serves as the primer for a specific DNA polymerase. In the priming reaction, a free TP first complexes with DNA polymerase at the telomeric origin. The DNA polymerase then catalyses the formation of a covalent bond between the free TP and a dNTP. This TP-linked dNTP becomes the 5' terminal nucleotide of the nascent strand, which can then grow to the end of its template.

Origin of linear DNA in bacteria

The *Borrelia* and *Streptomyces* plasmids have structures rarely described in prokaryotes, but replicons with these structures are widespread in eukaryotic cells and their organelles. There are three formal possibilities by which these similarities could have arisen: (i) descent from a common ancestor; (ii) convergence to fulfil similar functions, with no recent common ancestor; and (iii) 'borrowing', or a direct transfer from one organism to another (Diamond, 1990). At present there is no clear favourite among these, and more than one mechanism may have operated to produce similar genetic entities in phylogenetically diverse prokaryotes and eukaryotes.

Linear plasmids could have evolved from bacteriophages, as postulated for circular plasmids. A common phage or eukaryotic virus ancestor has been proposed for all the invertrons (Meinhardt *et al.*, 1990) and a few phages, such as ϕ29, have the same structure as *Streptomyces* linear plasmids. Borrelias harbour bacteriophages, but it is not known if borreliaphages have hairpin genomes like the N15 prophage (Barbour and Hayes, 1986). Although many bacteriophage genomes are linear double-stranded DNA, they typically have free 5' and 3' ends or self-complementary, single-stranded terminal overhangs.

Genetic exchange between prokaryotes and eukaryotes may have played a role in the dispersal of linear replicons. Two candidates for such a *trans*-kingdom transfer are *Borrelia duttoni* and the animal virus agent of ASFV. Both of these arthropod-borne pathogens are transmitted by the tick *Ornithodoros moubata*. The telomeric hairpin structures and sequences of the ASFV genome and *Borrelia* linear plasmids are similar, indicating that the *Borrelia* telomeres may have been acquired through a horizontal transfer from ASFV (Hinnebusch and Barbour, 1991).

The *Streptomyces* conjugative linear plasmids SLP2 and pBL1 can be transferred to different species (Chen *et al.*, 1993b; Zotchev *et al.*, 1992), and linear plasmids of related bacteria are transferred among different genera (Kalkus *et al.*, 1990). They may have strayed even farther afield. The organization and nucleotide sequences of some *Streptomyces* antibiotic synthesis genes are similar to those of certain fungi (Hara *et al.*, 1991). Genetic exchange between soil bacteria and fungi may account for this similarity (Weigel *et al.*, 1988), and Kinashi *et al.* (1992) hypothesized that *Streptomyces* conjugative linear plasmids were likely vehicles for this horizontal exchange.

Perhaps the most famous example of prokaryote–eukaryote gene exchange is the transfer of DNA from the phytopathogen *A. tumefasciens* into plant cells to induce crown gall tumour. A similar pathogenesis that involves a linear plasmid may occur with *R. fascians*, an unrelated plant pathogen. This Gram-positive organism causes leafy gall and contains a 4 Mb linear chromosome, as well as a 200 kb linear conjugative plasmid that carries the genes responsible for virulence (Crespi *et al.*, 1992).

Conversion between circular and linear forms

Since circular and linear molecules require different replication mechanisms, the two would appear to be evolutionarily distinct. However, a growing body of evidence suggests that linear variants can arise during replication of circular genomes. The genomes of mitochondria and chloroplasts seem to be particularly plastic in this regard. Circular and linear genomic isomers can coexist in the organelles of fungi, algae, and plant cells (Bendich and Smith, 1990). Mitochondria of the yeast *Pichia* have linear genomes with terminal hairpin loops, but circular monomeric forms are also present (Fukuhara *et al.*, 1993). Conversely, the chloroplast genomes of barley and rice are ordinarily circular, but linear hairpin deletion derivatives have been isolated from albino clones (Ellis and Day, 1986; Harada *et al.*, 1992). Fukuhara *et al.* (1993) found that species of two related yeast genera have either circular or linear mitochondrial genomes. Their physical and genetic maps are highly conserved, however, suggesting that the two forms diverged recently by a relatively trivial mechanism. There are simple models to explain the change from circular to linear DNA (Ellis and Day, 1986; Fukuhara *et al.*, 1993). Conversion might also occur by the action of a mobile DNA element. A transposon composed of two joined telomeres and the gene for a telomere-resolving enzyme could convert a circular molecule to a linear form by integration, cleavage, and telomere formation.

Bacterial linear plasmids and chromosomes may undergo similar transitions. Recently, a stably inherited circular derivative of one of the *Borrelia* linear plasmids was detected (M. S. Ferdows and A. G. Barbour, personal communication). A *Streptomyces* linear plasmid has also been shown to be able to replicate in either a linear or a circular form (Shiffman and Cohen, 1992), and although the *Streptomyces* chromosome may be linear, the *S. lividans* chromosome has a typical *oriC* that functions on circular minichromosomes (Zakrzewska-Czerwinska and Schrempf, 1992). Consistent with these findings, homologues of bacterial circular DNA replication genes have been detected on a *Streptomyces* linear plasmid and the *Borrelia* linear chromosome (Old *et al.*, 1992; Wu and Roy, 1993). In addition, a change from one telomere type to another has been documented for linear replicons. Cytoplasmic linear plasmids of the yeast *Kluyveromyces* are invertrons but, when introduced into *Saccharomyces*, they generate derivatives that have a hairpin loop at one end and a covalently bound terminal protein at the other end (Kikuchi *et al.*, 1985).

Linearization of circular replicons and at least transient stabilization of the free DNA ends occurs during replication, mobilization of conjugative plasmids, and integration and excision of phages and transposons. Many bacteriophages, including λ, have linear encapsidated genomes yet replicate as circles or concatemers (Furth and Wickner, 1983). Therefore, the distinction between circular and linear replicons may not always be absolute. Evidence for a linear genomic structure may often be dismissed as artefact but it may provide insight into the molecular biology of the replicon.

Significance of bacterial linear DNA

Whatever the origin of linear DNA in bacteria, this form may be maintained because of inherent advantages it provides. Telomeres are often recombinogenic because of reiterated sequences. In lower eukaryotes telomeric rearrangements and translocations provide a means for the duplication and molecular evolution of telomere-associated genes and gene families (Charron *et al.*, 1989). Recombination within a telomeric multigene family is responsible for most of the genetic differences seen among ASFV isolates (de la Vega *et al.*, 1990) and rearrangements among telomeric genes of poxviruses can extend host range (Buller and Palumbo, 1991). The *Borrelia* species that cause relapsing fever appear to have exploited this potential. These organisms escape the immune response of their mammalian host by switching expression among members of a family of antigenically distinct outer surface protein genes. These genes are located on linear plasmids and the promoter of the unique expression site is near a telomere. Antigenic variation results from the replacement of one gene with another at the telomeric expression site, a phenomenon very similar to outer-surface-protein gene switching in trypanosomes (Borst, 1991). Because they occur at the ends of linear molecules, these frequent rearrangements do not disrupt expression of any downstream genes (Kitten and Barbour, 1990).

Conjugation and chromosomal integration of *Streptomyces* linear plasmids and other invertrons may be simplified by their linear structure, since these processes generally require linear intermediates. In addition, possessing a type of conjugative element that is common to both prokaryotes and eukaryotes may allow genetic communication between actinomycetes, fungi, and plants in complex, competitive soil communities.

Future directions

Many questions about the molecular biology of bacterial linear plasmids and chromosomes remain unanswered. The telomeres of linear bacterial chromosomes have not yet been analysed. Genes, proteins, and DNA target sequences required for replication and segregation are undefined. An important step will be developing *in vitro* DNA replication systems, and genetic and biochemical studies of *Borrelia* plasmids may be simplified if coliphage N15-derived chimeric linear plasmids function in *E. coli*.

Reports of linear plasmids and chromosomes in bacteria are increasing and evidence is beginning to grow that some replicons may be maintained in both circular and linear forms. Understanding the molecular biology of linear genetic elements of bacteria and how these novel elements relate to circular replicons will lead to a more complete picture of the bacterial genome.

Note added in proof

Further evidence for the linear structure of the *Streptomyces lividans* chromosome is presented in the paper by Lin *et al.* (*Mol Microbiol*, 1993, **10:** 923–933 — this issue).

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