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Genesis of Antibiotic Resistance Crisis

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ABSTRACT

R plasmid isolated from an epidemic strain of *Shigella*in Tokyo is homologous to F plasmid of J. Lederberg's *E. coli* K-12. However, r-determinants of R6-5 are all transposons. Our data reports that an F-prime plasmid KLF-5 is a combination of F and chromosomal determinants arg-met joined by duplication of ƴ∂ in a direct order. In that respect, all antibiotic resistance determinants of R6-5 are similarly flanked by the duplication of IS1 in a direct order. F and R6-5 are compatible with two F-prime plasmids KLF-5 and F-prime Trp.

INTRODUCTION

This R plasmid is originated in 1960 following an outbreak of Shigellosis in Japan Tokyo when our miracle drug (Dr.Flemming's penicillin or ampicillin) has failed to give any relief. The patient's stool isolate confirms that the Gram-negative pathogen survives even in ampicillin (1-3). Similar reports keep coming from many industrially developed countries where antibiotics are sold, not without physician's prescriptions. We must accept the truth that an industrially developed country Japan is responsible for the evolution of R plasmid by an overuse of antibiotics in diarrheal diseases (4, 5 Watanabe). Subsequently, many reputed investigators have spent almost a decade to completely characterize this R plasmid both physically and genetically (6-9).

MATERIALSAND METHODS

A part of this work has previously been published (10). R6-5, a spontaneous variant of R6 that lacks tetracycline resistance, was isolated in our laboratory (11). Specimens were prepared by modifications of the Kleinschmidt technique and were examined on a Philips EM-300 electron microscope.

RESULTS

In order to understand the origin of R-plasmid, we want to compare it with F-prime plasmids. This knowledge is essential to understand the genesis of R-plasmid and subsequently antibiotic resistance crisis. Fig. 1 shows a comparison between F plasmid and R plasmid.

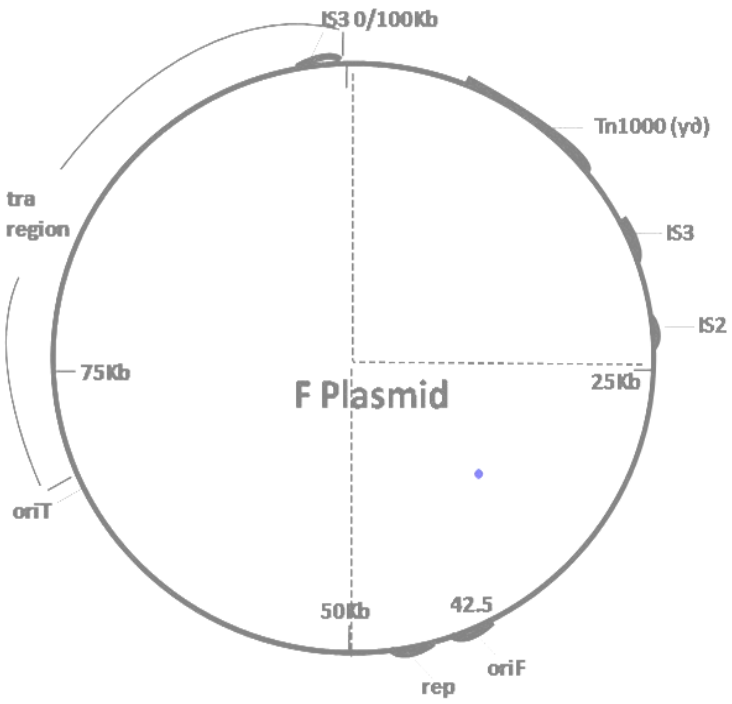

Fig1 a. F-plasmid and R plasmid are compared to support that RTF component of R plasmid and F plasmid are the same. R-det is absent in F

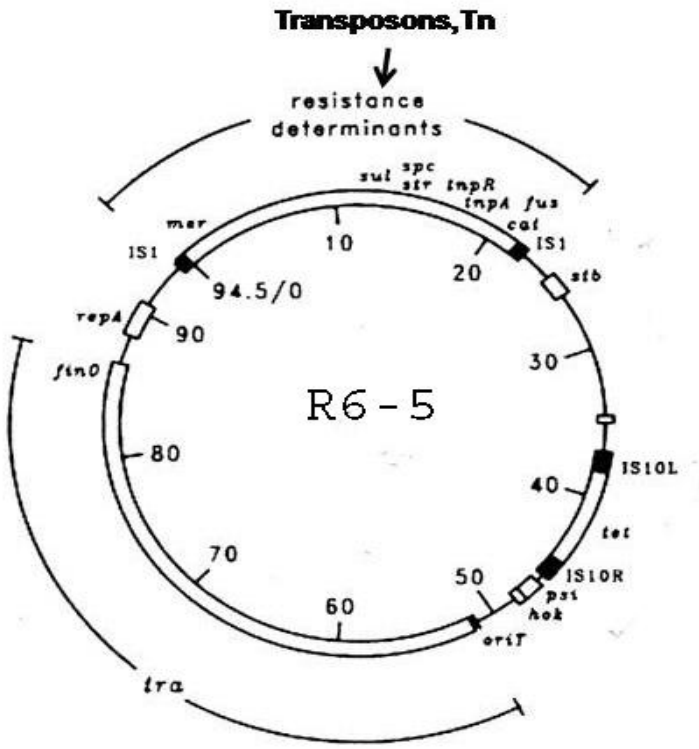

Fig.1 b. R Plasmid R6-5 carries r-det which is a collection of transposons.

The kilobase coordinate begins at the clockwise end of insertion sequence IS/b in R6-5 and at the counterclockwise end IS3 in F. The F genome is divided into two components - antibiotic resistance determinant (r-det), 93 Kb through 23 Kb and RTF. r-determinant is flanked by direct repeats of the IS1 sequence. RTF and F appear to carry common repA functions. Still, there is the difference of 9 base sequence and therefore they are compatible (9, 17)

F-prime plasmid and R plasmid R6-5 should be compared to understand the genesis of antibiotic resistance transposons Tn1, Tn2, Tn3 and so on. In 1976, Professor Werner K Maas and Professor Sunil Palchaudhuri have previously published this work. However, re-interpretation is necessary to appreciate how this F-prime plasmid resembles R plasmid, R6-5. Unfortunately, R6-5 has been abused by the gene cloners from 1972 without the knowledge that r-det is a transposon. Professor SN Cohen and coworkers have spread the transposons globally by abuse of *in vitro* gene cloning experiments (14-16). Analysis of F-prime plasmid KLF-5 leads to a conclusion that probably R plasmid has been formed in the same way. Fig. 2 shows that F-prime carrying arg and met operons is highly unstable (9). It dissociates into two components like R6-5. One is carrying the chromosomal segment flanked by y∂ sequences in a direct order and the other one is a complete F-plasmid (100 Kb long). The chromosomal segment does not carry any replicon but is capable of integrating into an F plasmid for its multiplication. This chromosomal component carrying arg and met operons is flanked by a Transposon 1000 or y∂ in a direct order. So we conclude that IS1 known as IS sequence, but y∂ is known both as IS sequence or transposons.

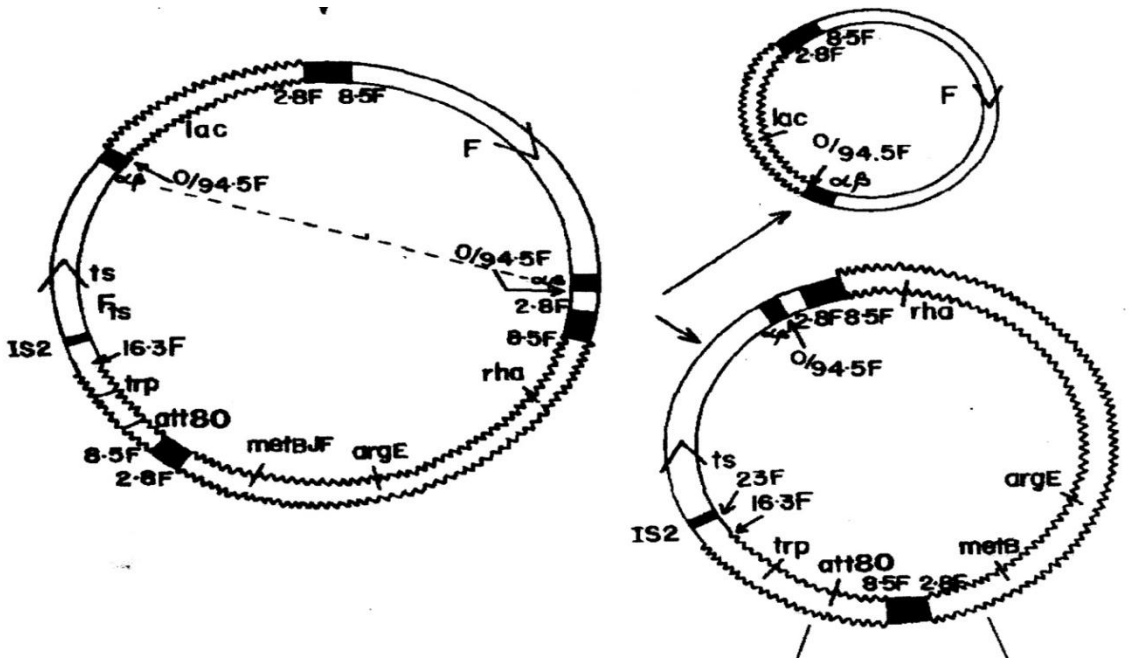

Fig. 2. KLF-5 plasmid dissociated two components:

A complete F plasmid and a chromosomal segment carrying ArgMetTrp but having no replicon. This provides a clue how the R plasmid is formed by the combination of RTF and r-det carrying several transposons.

DISCUSSION

In order to understand the origin of R-plasmid we strongly believe that F plasmid carrying both IS and Tn DNA elements is the forerunner. Retrovirus is no exception. It belongs to the same group of mobile DNA elements. Interestingly y∂ targets *E. coli K*-12 origin of the replicon. As a result, some Hfr strains, Ra1 and Ra2 as reported by B Low, formed by the integration of F via y∂ is highly unstable (17, 18). Significantly the F-prime plasmid KLF5 formed by the Hfr is also unstable. In 1976, we have published this data in a famous journal MGG (9). This knowledge is essential to understand the genesis of R-plasmid and subsequently antibiotic resistance crisis. However self-transmissible plasmids, both F and R6-5 have the same replicon and tra genes. Interestingly, these two plasmids are compatible but two F-primes – F-prime KLF5 and F-prime trp are incompatible (9). In full agreement with Professor W. K. Maas, we have confirmed 9 base pairs in dnaA region of F is absent in R6-5 (19). This difference appears to be responsible for the compatibility between F and R6-5 (20-22).

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