Filamentous phages of Ralstonia solanacearum: double-edged swords for pathogenic bacteria

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Some phages from genus Inovirus use host or bacteriophage-encoded site-specific integrases or recombinases to establish a prophage state. During integration or excision, a superinfective form can be produced. The three states (free, prophage, and superinfective) of such phages exert different effects on host bacterial phenotypes. In Ralstonia solanacearum, the causative agent of bacterial wilt disease of crops, the bacterial virulence can be positively or negatively affected by filamentous phages, depending on their state. The presence or absence of a repressor gene in the phage genome may be responsible for the host phenotypic differences (virulent or avirulent) caused by phage infection. This strategy of virulence control may be widespread among filamentous phages that infect pathogenic bacteria of plants.

Keywords: filamentous phage, integration, phytopathogen, Ralstonia solanacearum, virulence change

Filamentous phages and pathogenic bacteria

Bacteriophages belonging to the genus Inovirus are filamentous particles containing a circular single-stranded (ss) DNA genome. Infection with this kind of phage does not cause host cell lysis, but establishes a persistent association between the host and phage, producing and releasing phage particles from the growing and dividing host cells. In general, the genome of inoviruses, represented by Escherichia coli F-plasmid-specific phage Ff (F1, fd or M13), is organized in a modular structure, in which functionally related genes are grouped together (Horuchi et al., 2009; Rakonjac et al., 2011). Three functional modules are always present: the replication module, the structural module, and the assembly and secretion module. The replication module contains the genes encoding rolling-circle DNA replication and single-strand DNA (ssDNA) binding proteins gII, gVII, and gX (Horuchi et al., 2009). The structural module contains genes for the major (gVII) and minor coat proteins (gIII, gVI, gVII, and gX), and gene gII encodes the host recognition or adsorption protein pII (Wang et al., 2006). The assembly and secretion module contains the genes for morphogenesis and extrusion of the phage particles (gII and gV; Marvin, 1998). Gene gV encodes protein pV, an aqueous channel (secretin) in the outer membrane, through which phage particles exit from the host cells (Marciano et al., 1999). Some phages encode their own secretins, whereas others use host products (Davis et al., 2009). Because inoviruses coexist with their host cells, infection by these phages can mediate conversion of the host bacterial phenotypes in various ways. In pathogenic bacteria of either animals or plants, virulence is frequently affected by phage infection. For example, infection of Xanthomonas campestris pv. oryzae NP5850 by the filamentous phages Xi and Xu enhanced virulence, possibly because of overproduction of extracellular polysaccharides (EPS) by the phage-infected bacterial cells (Kamiunten and Wakimoto, 1982). Tieng et al. (1990) also reported that infection of X. campestris pv. campestris by the filamentous phage Lf increased virulence by promoting EPS production. Filamentous phages are assembled at the host cell surface and secreted into the environment. However, once then cells form colonies on the semi-solid medium (and possibly within the liquid medium), some fractions of secreted phage population are bound to stay trapped in the colony, potentially accumulating to high concentrations and forming a matrix surrounding the cells in the colony. These trapped phage particles may serve to cross-link cells to give high densities and induce biofilms. This situation was reported for small colony variant formation in Pseudomonas aeruginosa depending on phage Pf4 activity (Welsh et al., 2004; Rice et al., 2009). More direct involvement of filamentous phages in host virulence is well characterized in Vibrio cholerae. The pathogenicity of this severe diarrheal disease-causing bacterium depends on two key virulence factors, the toxin co-regulated pilus (TCP) and cholera toxin. Cholera toxin genes are encoded on the filamentous phage CTXφ and introduced into bacterial cells by phage integration mediated by the host difN/RecA recombination system (Huber and Waldor, 2002; Davis and Waldor, 2003). In Ralstonia solanacearum, infection by φRSS1 induced the early expression of pchA, a global virulence regulator, and also enhanced twitching motility (Addy et al., 2012b). Contrastingly, with these virulence-enhancing effects of φRSS1, loss of virulence was also reported in R. solanacearum. R. solanacearum completely lost virulence through infection with two other filamentous phages φRSM1 and φRSM3 (Addy et al., 2012a). Many virulence factors were significantly reduced in...
φRSS-infected cells. These opposing effects of different filamentous phages on R. solanacearum virulence makes it an ideal study model system for understanding the effect of filamentous phage on their hosts. Here we will describe the role of filamentous phage in the virulence of R. solanacearum and suggest a causative relationship between a phage-encoded transcriptional repressor and R. solanacearum pathogenicity.

**Ralstonia solanacearum AND BACTERIAL WILT**

*R. solanacearum* is a Gram-negative β-proteobacterium that causes bacterial wilt disease in many important crops including tomato, potato, tobacco, and eggplant. Because of its wide geographic distribution and unusually broad host range (more than 50 plant families), it is responsible for significant crop losses worldwide (Hayward, 2000). Once the bacteria enter a susceptible host, they colonize the intercellular spaces of the root cortex and vascular parenchyma. The bacteria eventually enter the xylem and spread into the upper parts of the plant, causing wilt (Vasse et al., 2000; Kang et al., 2002; Vao and Allen, 2007). The development of bacterial wilt disease depends on bacterial pathogenicity and virulence (Carney and Denny, 1996; Denny, 2006). R. solanacearum virulence is additive, complex, and involves the production of multiple virulence factors (Schell, 2000; Genin and Boucher, 2002). For example, exopolysaccharide I (EPSI), a large nitrogen-rich acidic exopolysaccharide (Lavie et al., 2002), is thought to be an important virulence factor. It enhances the speed and extent of stem infection spreading from the root (Sale et al., 1997) and is presumed to cause wilting by restricting water flow through xylem vessels (Garg et al., 2000). In addition to EPSI, *R. solanacearum* secretes enzymes that degrade the plant cell wall through the type II secretion system (T2SS). Pectinolytic enzymes fragment plant xylem into oligomers, which act as a substrate for bacterial growth (Tans-Kersten et al., 2001). The breakdown of pectin enhances virulence by facilitating bacterial movement through pectin-rich regions such as vascular bundles (Gonnazal and Allen, 2003). Cellulolytic enzymes also facilitate bacterial invasion of roots and/or penetration of xylem vessels by degrading cellulose glucans in the cell wall (Liu et al., 2003). In addition to T2SS-meditated secreted proteins, the type IV pilus (Tip) is believed to be another virulence factor of *R. solanacearum* (Davis and Waldor, 2003). This protein forms a surface appendage that is responsible for twitching motility and polar attachment to host cells or to plant roots, and enhances the severity of wilt disease (Liu et al., 2001; Kang et al., 2002).

Expression of the pathogenesis and virulence genes in *R. solanacearum* is controlled by a complex regulatory network (Schell, 2000; Genin and Boucher, 2002; Denny, 2006) and is drastically affected by various environmental factors. The regulation is outlined as follows: the transcriptional regulator PhcA plays a critical role in the regulatory network. Abundant PhcA activates production of multiple virulence factors such as EPSI and cell wall degrading enzymes (CWDE). PhcA is activated by a quorum sensing system mediated by the two-component regulatory system PhcS/PhcR that responds to threshold levels of 3-OH palmitic acid methylester (3-OH PAME), an autoinducer of quorum sensing that controls virulence. Therefore, the levels of 3-OH PAME, cell density, as well as cell surface nature all affect virulence in *R. solanacearum*.

**THREE STATES OF FILAMENTOUS PHAGE φRSS WITH DIFFERENT EFFECTS ON HOST VIRULENCE**

φRSS was isolated from a soil sample collected from tomato crop fields (Yamada et al., 2007). φRSS1 particles have a flexible filamentous shape 1,100 ± 100 nm in length and 10 ± 0.5 nm in width, giving a morphology resembling coliphage F (M13, F or fd; Buchen-Osmond, 2003; ICTVdB). The φRSS1 particles contain a ssDNA genome (6,662 nt; DDBJ accession no. AB259124), with a GC content of 62.6%. There are 11 open reading frames (ORFs), located on the same strand (Figure 1A). The φRSS1 gene arrangement is consistent with the general arrangement of Ff phages. Genomic Southern blot hybridization showed several examples of φRSS1-related sequences integrated in the genomes of various *R. solanacearum* strains (Yamada et al., 2007). A φRSS1-related phage (designated φRSS0) was induced and isolated from one such cross-hybridizing strain (C319) by infection with another phage (jumbo phage φRSS1). The DNA sequence of φRSS0 was very similar to φRSS1, but contained an extra 626 nt at φRSS1 position 6,628, next to the integenic region (IG), giving an entire genomic size of 7,288 nt (GenBank accession no. JQ408219). Within the φRSS0 extra region, an ORF (ORF13) of 468 nt, corresponding to 156 amino acid residues, in a reversed orientation compared with the other ORFs, was found (Figure 1A). The amino acid sequence of ORF13 showed similarity to DNA-binding phage transcriptional regulators (accession no. B5SCX5, E-value = 1e-29).

Using inverse PCR with the new phage nucleotide sequences as primers, the prophage (φRSS0)-junctions (attL and attR) in strain C319 were obtained and their nucleotide sequences determined. It was found that both attL and attR contained repeated elements, corresponding to the 5′-sequence of *R. solanacearum* GM11000 (Carney and Roten, 2009). This repeated sequence, 5′-ATTTT AACAT AAGAT AAAT-3′ (designated attRSS0)-junctions (Huber and Waldor, 2002). ORF13 encoded a GC content of 62.6%. There are 11 open reading frames (ORFs), was found (Figure 1A). The amino acid sequence of ORF13 showed similarity to DNA-binding phage transcriptional regulators (accession no. B5SCX5, E-value = 1e-29).

Upon infection by the φRSS1 phage, the host *R. solanacearum* cells showed several abnormal behaviors, including less turbidity and frequent aggregation in the liquid culture, less coloration of colonies on plates, and a decreased growth rate (approximately 60% of the normal rate). More interestingly, φRSS1-infected cells showed enhanced virulence on tobacco (Yamada et al., 2007) and tomato plants (Addy et al., 2012b). In the case of strain C319 (φRSS0 lysogenic), inoculated tobacco plants showed withering symptoms of grade 2–3 at 14 days post-inoculation (p.i.), whereas tobacco plants inoculated with φRSS1-infected C319 cells

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FIGURE 1 | φRSS type filamentous phages infecting R. solanacearum. (A) Genomic organization of φRSS1 and φRSS0 (Kawasaki et al., 2007; Yamada, 2011) shown in a linear form. ORFs or genes are represented by arrows oriented in the direction of transcription. The functional modules for replication (R), structure (S), and assembly secretion (A-S) are indicated according to the M13 model (Marvin, 1998). The region containing the attP sequence is also indicated. (B) Interrelationship between three states of φRSS phages. The phage genomic DNA is shown in a circular form where most genes are not shown. φRSS0 is equipped with a 626-nt element containing ORF13, within which attP(dif) is located. This element is missing in φRSS1. The processes of interconversion between φRSS0 and φRSS1 are not known. φRSS0 is integrated at the dif site (attB) on the host genome. The prophage state is shown as RSSφ, where the left and right borders are indicated as attL and attR, respectively. This integration (reversible) is mediated by the host XerCD system. φRSS1 may be produced directly from RSS0φ. The three states of φRSS0-type phage (φRSS0, φRSS1, and φRSS0 prophage) affect host R. solanacearum cells differently after infection, especially in host virulence. Compared with wild-type virulence (+), φRSS1 enhances (++) and φRSS0 reduces (−) the host virulence.

Effects on host virulence by infection with φRSS0 in its free form (not prophage) were also examined. To make wilting symptoms clearer, tomato-tropic R. solanacearum strain (MAFF 106603) in tomato experimental system was used. The cells were infected with either φRSS0 (free) or φRSS1. The physiological features of φRSS0-infected R. solanacearum MAFF 106603 cells were almost the same as φRSS1-infected MAFF 106603 cells, except that the φRSS0-infected cells formed colonies of more mucoid appearance on CPG plates. When MAFF 106603 (wild-type) cells were inoculated into the major stem of tomato plants, all 12 plants showed wilting symptoms as early as 3 days p.i. and died 5–7 days p.i. φRSS1-infected cells of MAFF 106603 inoculated into tomato in the same way caused wilting earlier, at 2 days p.i., and all 12 plants died by 5 days p.i. In contrast, tomato plants inoculated with φRSS0-infected cells showed wilting symptoms much later: most plants (10 of 12) survived after 7 days and a few plants did not show any symptoms until 23 days p.i. Therefore, φRSS0 infection caused reduced virulence in host bacterial cells (Tasaki et al., unpublished). The virulence-enhancing effects by φRSS1 infection can be explained as follows: surface-associated φRSS1 particles (or phage proteins) may change the surface nature (hydrophobicity) of host cells to generate a high local cell density, resulting in early activation of phcA, the global virulence regulator, or lack of orf13, which is absent from the φRSS1 genome (Addy et al., 2012b). The reduced virulence observed for φRSS0-infected cells may be caused by the function(s) of ORF13 encoded by φRSS0. These results are summarized in Table 1.

Table 1  Three states of filamentous phages and their effects on host virulence.

| Phage state       | φRSS-type | φRSM-type | Virulence |
|-------------------|-----------|-----------|-----------|
| Free              | φRSS0     | φRSM3     | ++/- or − |
| Prophage          | RSSφ      | RSMφα     | +         |
| Superinfective mutant | φRSS1 | φRSM3-ΔORF15 | ++       |

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A GC content of 59.9%. There are 12 putative ORFs located on the same strand and three on the opposite strand. The φRSM1 genes are shown in Figure 2A, in comparison with the conserved gene arrangement of M13-like phages (Kawasaki et al., 2007). Here, ORF13, ORF14, and ORF15 (reversely oriented) are inserted between ORF12, corresponding to pII as a replication protein, and ORF1, corresponding to a DNA-binding protein like pV, in the putative replication module. ORF13, ORF14, and ORF15 show amino acid sequence similarity to a proline-rich transmembrane protein, a resolvase/DNA invertase-like recombinase, and a putative phage repressor, respectively (Kawasaki et al., 2007; Addy et al., 2012a). There are two additional ORFs (ORF2 and ORF5) between the replication and structural modules. The functions of these ORF-encoded proteins are not known. In genomic Southern blot hybridization, two different types of φRSM1-related prophage sequences were detected in R. solanacearum strains. Strains of type A include MAFF211270 and produce φRSM1 itself, and strains of type B (giving different restriction patterns) are resistant to φRSM1 infection, but are susceptible to φRSM3 (see below). By determining the nucleotide sequences of junction regions of the φRSM1-prophage in the MAFF 211270 chromosomal DNA, an attP/attB core sequence was identified as 5'-TGGCGGAGGCGG-3', corresponding to positions 8,544-8,556 of φRSM1 DNA, located between ORF14 and ORF15. Its nucleotide sequence is identical to the 3'-end of the host R. solanacearum gene for serine tRNA(UUC) in the reverse orientation. A φRSM1-like prophage (type B) in strain MAFF 730139, designated φRSM3, was obtained by PCR amplification using appropriate primers containing these att sequences (Askora et al., 2009). Compared with the φRSM1 genome, the φRSM3 prophage sequence (8,929 nt) is 75 nt shorter. The sequences show 93% nucleotide identity and major differences are found within two regions; positions 480-660 and positions 2,500-3,000 in the φRSM1 sequence. The former region corresponds to ORF2, which is inserted between the replication module (R) and the structural module (S), and has no similarity between the two phages. The latter falls into the possible D2 domain of φRSM3, which is almost the same as φRSM1, as shown in Figure 2A.

As described above, the genomes of φRSM phages are sometimes integrated in the host genome. Askora et al. (2011) demonstrated that the integration is mediated by the phage-encoded recombinase (ORF14 of φRSM1/φRSM3), which has significant homology to resolvase/DNA invertases (small serine recombinases), with attP/attB corresponding to the 3'-end of the host serine tRNA(UUC) gene in the reverse orientation. This is the first case of filamentous phages demonstrated to integrate into the host genome by its endogenously encoded integrase (Askora et al., 2012). The same unit of integration (φRSM Int(attP)φ) was found in a Ralstonia pickettii 121 phage and in Burkholderia pseudomallei 668 prophages (Askora et al., 2012). Together with these phages, it would not be surprising if similar Int-containing filamentous phages occur widely in nature.

Infection by φRSM1 or φRSM3 establishes a persistent association between the host and the phage. Upon infection by φRSM phages, the host cells showed some abnormal behaviors and characteristics, such as frequent aggregation, dark coloration, and relatively small colony size, as observed in φRSS infection. When cells of MAFF 106611 (φRSM3 lysogenic strain) or MAFF 106603 (not lysogenic) were inoculated into tomato plants, all 20 plants showed wilting symptoms as early as 3 days p.i., whereas none of the 20 tomato plants inoculated with free-φRSM-infected cells (for example, MAFF 106603) showed any wilting symptoms until 4 weeks p.i. (Addy et al., 2012a). This loss of virulence effect of φRSM3 infection can be explained in three ways: (i) reduced twitching motility and reduced amounts of type IV pilus (Tlp), (ii) lower levels of β-1,4-endoglucanase (Egl) activity and EPS production, and (iii) reduced expression of certain virulence/pathogenicity genes (egf, pohC, pheA, pheK, pilF, and hrpB) in the infected cells (Addy et al., 2012a). This is supported by restoring virulence in φRSM3 lysogen by deletion of φRSM3-encoded orf5, the gene for a putative repressor-like protein, was disrupted (Addy et al., 2012a). Therefore, ORF5 of φRSM3 may repress host genes involved in pathogenicity/virulence and consequently result in loss of virulence. With different strains as hosts, φRSM also gave similar results. The φRSM states and interaction with the host genome can be depicted similarly to φRSS phages, as shown in Figure 2B. These results are summarized and compared with the three states of φRSS in Table 1.

PERSPECTIVE AND HYPOTHESIS

As seen here, for R. solanacearum, filamentous phages such as φRSS and φRSM are double-edged swords; sometimes they help bacteria to infect plants by enhancing bacterial virulence, and sometimes they interrupt bacterial infection of plants by repressing host genes involved in virulence. The contradictory effects of these phages may largely depend on the presence or absence of a phage-encoded regulatory protein. Two questions arise here: (i) How does the regulatory affect on the host genes; working alone, with other phage factors, or with host factors? (ii) How does such a regulatory gene become acquired by or lost from the phage genome? Concerning the first question, as shown in Figure 1B, attP is located within ORF13 on φRSS DNA, and after integration at attB on the host genome, a truncation of ORF13 (at the C-terminus) occurs. By creating a new stop codon in the reading frame, the size of ORF13 reduced from 156 to 130 aa with a 26-aa truncation at the C-terminus (Tasaka et al., manuscript in preparation). A DNA-binding motif (Helix-Turn-Helix) is located in the N-terminal moiety and the C-terminal region may have some regulatory function (such as ligand-binding). This suggests a functional difference of the ORF13 protein before and after integration. One possibility is that the full length ORF13 (ORF15 in φRSM phages) expressed from free phages may function to preferentially regulate host genes and the truncated (or modified) form expressed from the prophage may function to stabilize the prophage state and phage immunity, protecting against infections by related phages (Hypothesis 1). This hypothesis is compatible with similar Int-containing filamentous phages occur widely in nature.
with the observation that once a φRSS and φRSM prophage state was established, the phage genomic DNA and phage particles seldom appeared in the lysogenic strains. Like φRSM, the DNA or the phage particles are not identified in the lysogen, even though the orf15 encoding the putative repressor ORF15 is not changed before and after the host integration. Because ORF14 integrates (serine recombinase) of φRSM phages likely mediates both integrative and excessive recombinations (Askora et al., 2011), some additional factors are required to mediate prophage replication or excision. The function, regulatory mechanism, and effect on virulence of φRSS orf13 or φRSM orf15 remain to be investigated by direct expression of the corresponding gene in an appropriate host strain. In our preliminary trial where the coding region of ORF15 of φRSS3 (ORF13 of φRSS0) was expressed from a plasmid under the control of lacP and introduced into appropriate host strains, no transformants with a correct construct appeared (colonies that appeared on the selection plates after transformation all contained deleted inserts). One of the explanation for this is putative toxic effect of ORF13 and ORF15 on the host when expressed under these conditions. Some additional factors encoded on the phage genome may be involved in the appropriate regulation, interacting with ORF13 or ORF15 (Hypothesis 2). Further studies with mutated constructs of ORF13 or ORF15 are required to test these hypotheses.

As for question of loss of a repressor protein, a 626-nt sequence unit containing orf13 and attP detected in φRSS0 and missing from φRSS1 plays a crucial role in φRSS dynamics. The origin of such a sequence and the mechanism how it comes in or out of the phage are largely unknown. However, the possibility of two forms from a phage is important. Apparently, φRSS1-infected bacterial cells have an advantage in the pathogenic lifestyle. Nevertheless, the virulence is not always necessary for this soil-borne bacterium. Infection of φRSS0 provides the host cells with a sophisticated mechanism to control their virulence. Similar mechanisms may function in other pathogenic bacteria (Hypothesis 3). To test this hypothesis, various systems involving pathogenic bacteria and their filamentous phages should be examined. For example, φRSS1-like superinfective phage G1tv spontaneously appeared from the C01 lysogenic strain of Xanthomonas campestris pv. citri (Kuo et al., 1994). Unfortunately, nucleotide sequence information is not available for this phage. Similar kinds of phage involvement in host virulence regulation may be universal, because φRSS- or φRSM-related sequences are frequently found in various bacterial genomic sequences in the databases, including R. pickettii...
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