Geminiviridae

Secondary article

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The *Geminiviridae* are a group of plant viruses with small, circular, single-stranded DNA genomes encapsidated in particles that have a twinned quasi-icosahedral (geminate) shape, from which the family derives its name. They are pathogens of cereals, vegetable and fibre crops, and pose a serious threat to agriculture worldwide.

Article Contents

Historical Perspective

Long before geminivirus diseases were recognized, some infected plants were selected and cultured for their pleasing vein yellowing and mosaic symptoms. It is believed that the first reference to a geminivirus disease occurs in a poem in the classic anthology *The Manyoushu* in the year 752 by Empress KoKen of Japan, describing the beautiful yellowing of the leaves of a plant thought to be *Eupatorium chinensis*. A striking example of a mosaic is seen in *Abutilon sellovianum* infected with *Abutilon mosaic virus* (AbMV), an infected plant having been introduced into Europe from the West Indies in 1809.

Around the turn of the century, several diseases were reported which are now known to have geminiviral aetiology: a cassava mosaic disease in East Africa was described in 1894, a serious outbreak of beet curly top disease occurred in California, USA in 1899, and maize streak disease in South Africa was recorded in 1901. We now know that these are caused by *African cassava mosaic virus* (ACMV, synonym cassava latent virus), *Beet curly top virus* (BCTV) and *Maize streak virus* (MSV), respectively. Around 1915, the insect responsible for transmission of beet curly top disease was identified as the leafhopper *Eutettix tenella*, now called *Circulifer tenellus*, and it was shown that maize streak disease was transmitted by a leafhopper, *Cicadulina mbila*. Five years later, crop losses of cassava in East Africa again drew attention to cassava mosaic disease, which was shown to be transmitted by whiteflies (*Bemisia tabaci*). Increasing numbers of disease outbreaks maintained scientific interest, leading to the purification and electron microscopy of novel virus particles in 1974. This was followed by the exciting and unexpected discovery in 1977 that ACMV and MSV have circular, single-stranded (ss)DNA genomes (Harrison *et al*., 1977). These novel characteristics led to the proposal of a new virus group which was officially accepted by the International Committee for Virus Taxonomy in 1978. The cloning and sequence analysis of ACMV in 1983 and MSV in 1984 heralded the start of an intensive investigation of geminivirus molecular biology.

Because they have small DNA genomes, the isolation and molecular characterization of many geminiviruses has proceeded rapidly, and revealed the existence of a diverse range of species and strains. The genomes encode a limited number of genes, implying that they are heavily dependent on host functions for their proliferation. Indeed, their need to manipulate the host cell cycle to provide an environment suitable for their replication has recently been recognized. Just as DNA tumour viruses have proved invaluable in the study of animal cellular functions, it is anticipated that the functional analysis of geminivirus genes will contribute to our understanding of plant cellular processes involved in the regulation of gene expression and DNA replication, and in cellular communication. It is likely that this fundamental knowledge will find application in the production of crops that are resistant to disease and for crop improvement in general.

Classification Including Prominent Members

The family *Geminiviridae* contains diverse viruses that have been classified into three genera (*Mastrevirus*, *Curtovirus* and *Begomovirus*) on the basis of their genome organization (**Figure 1**) and vectors (Briddon and Markham, 1995). Mastreviruses have monopartite genomes, and each member is usually transmitted by a single species of leafhopper. The majority infect monocotyledonous plants of the family Poaceae (e.g. the type member MSV, and *Wheat dwarf virus* (WDV)). Some (e.g. *Bean yellow dwarf virus* (BeYDV)) infect only dicotyledonous plants (Leguminosae and Solanaceae), but all members share a similar genome organization. Curtoviruses are transmitted either by leafhoppers (e.g. the type member BCTV) or in one case (*Tomato pseudo-curly top virus* (TPCTV)) by a treehopper, and can infect a wide range of dicotyledonous plant species. They also have monopartite genomes, but these show fundamental differences in their organization from the mastrevirus genomes. The majority of geminiviruses

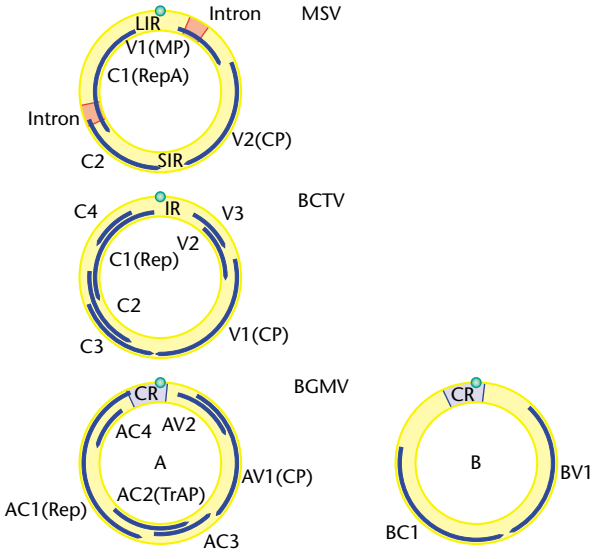

Figure 1 Genome organization of type members of the three *Geminiviridae* genera. The position and orientation of virion-sense (V) and complementary-sense (C) genes of MSV (genus *Mastrevirus*), BCTV (genus *Curtovirus*) and BGMV (genus *Begomovirus*) are shown in relation to the initiation site of virion-sense DNA replication, located within the conserved nonanucleotide TAATATT↓AC (green dots). MSV contains two noncoding regions referred to as the large and small intergenic regions (LIR and SIR, respectively), and two introns (red boxes). The two genomic components of BGMV (DNAs A and B) contain an almost identical sequence of approximately 200 nucleotides referred to as the common region (CR; blue boxes) located almost entirely within the intergenic region (IR in BCTV).

belong to the genus *Begomovirus* (the type member is *Bean golden mosaic virus* (BGMV), but ACMV, *Tomato golden mosaic virus* (TGMV) and *Tomato yellow leaf curl virus* (TYLCV) have all been studied intensively). All are transmitted by whiteflies and collectively infect a wide range of dicotyledonous plants although, individually, their host ranges are relatively narrow. The majority have bipartite genomes (DNAs A and B), although some (e.g. TYLCV) have monopartite genomes resembling DNA A.

Within each genus, viruses have been classified as either distinct species, strains or isolates on the basis of differences in biological characteristics such as host range, tissue tropism and pathogenicity, immunology, diversity of their DNA sequences, and functional compatibility of gene products.

Structure of Virus Particles

Most of the information about virus particle structure comes from studies by Hatta and Francki (1979) on *Chloris striate mosaic virus* (CSMV). Sucrose gradient profiles of purified virus showed that the major component had a sedimentation coefficient of approximately 70 S. Electron microscopy showed this to comprise 18 × 30 nm geminate particles. Each particle has a central electron-dense cleft, approximately 1.7 nm wide, which is visible between the two halves of the twinned structure and produces a waist-like appearance (**Figure 2a**).

The relative molecular weight of CSMV geminate particles is about 3.8×10^6. Modelling studies and electron microscopy suggest that the geminate particle consists of two incomplete icosahedra with a T = 1 surface lattice having 22 capsomeres, each approximately 8 nm in diameter and estimated to contain five capsid protein (CP) molecules. Gel electrophoresis of purified CSMV identified a 27.9-kDa protein, although more recent sequence analyses show that geminivirus CPs range from 27 to 34 kDa. Geminate particles contain circular ssDNA (**Figure 2b**); the buoyant density of CSMV geminate particles in caesium chloride indicates that they contain approximately 19% DNA, equivalent to the presence of one copy of ssDNA of 2.5–3.0 kb in size. Some geminivirus preparations contain 18-nm-diameter icosahedral particles which are likely to encapsidate approximately half-size defective ssDNA (**Figure 2b**); larger particles comprising three or four quasi-icosahedra may also be seen.

Electron microscopic examination of thin sections of geminivirus-infected tissue has demonstrated geminate particles aggregated in the nuclei of infected cells, occasionally in regular paracrystalline arrays.

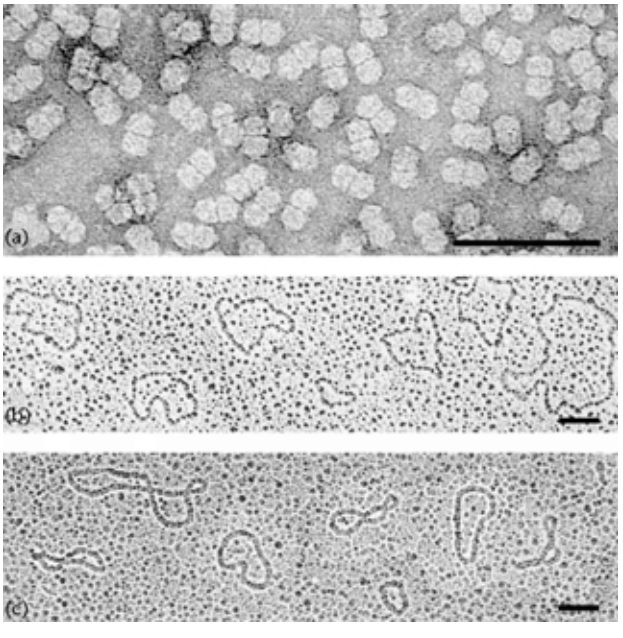

Figure 2 Electron micrographs of (a) purified MSV particles showing their characteristic twinned (geminate) morphology, (b) ACMV encapsidated circular ssDNA, and (c) ACMV circular dsDNA, the replicative form of the viral DNA. In addition to the predominant monomeric DNA of approximately 2.8 kb, examples of dimeric DNAs and half-size defective DNAs are evident. Bar, 100 nm.

Gene Expression and Function

Transcription

Transcription of the geminivirus genome is bidirectional, with the majority of transcripts initiating from RNA polymerase II-type promoters within, or proximal to, the intergenic region (IR), large intergenic region (LIR) or common region (CR) (**Figure 1**), to produce 3′ coterminal complementary-sense and virion-sense transcripts. All mastreviruses produce both spliced and unspliced complementary-sense transcripts. This mechanism enables the synthesis of C1 (RepA) protein from the unspliced transcript and C1:C2 (Rep) protein from the spliced transcript (**Figure 1**). Recently, it has been shown that splicing features in MSV and *Digitaria streak virus* virion-sense gene expression, an intron being present within gene *V1*, which encodes the movement protein (MP, **Figure 1**). Only unspliced transcripts are able to produce MP; splicing may also enhance expression of the downstream *CP* gene (Palmer and Rybicki, 1998).

There is no evidence for splicing of begomovirus and curtovirus transcripts. The transcription maps of distinct viruses within these genera may differ slightly, reflecting variation in their gene complement. For example, for virion-sense gene expression, TGMV has a single predominant transcript for CP expression, ACMV has two overlapping transcripts suitable for CP and AV2 protein expression, and BCTV has at least three overlapping transcripts for CP, V2 and V3 protein expression. Transcripts are believed to be largely monocistronic, although begomovirus AC2 and AC3 proteins may be expressed from a single transcript.

The pattern of overlapping genes and multiple transcription initiation points, the presence of polycistronic and inefficiently spliced transcripts (for mastreviruses), and overlapping 3′ termini of virion-sense and complementary-sense transcripts imply that gene expression is highly regulated.

Replication-associated proteins

At the onset of infection, ssDNA is first copied to produce a circular double-stranded (ds)DNA intermediate (**Figure 2c**), a process that requires only host proteins. The dsDNA then acts as a template for transcription and rolling circle replication (Bisaro, 1996). The replication-associated protein (Rep) is the only virus protein absolutely required for viral DNA replication, and is multifunctional. It initiates rolling circle replication by introducing a site-specific nick in the virion-sense DNA strand within the nonanucleotide sequence TAATATT$^{\downarrow}$AC found in all geminiviruses (**Figure 1**), and mediates circularization of the nascent ssDNA to complete the replication cycle. Begomovirus and curtovirus AC3 (C3) protein is not essential for infectivity but appears to act as a replication enhancer, possibly by interacting with Rep. Rep has no polymerase activity, but recent evidence suggests that it stimulates cells to enter S phase to facilitate viral DNA replication. Curtovirus C4 protein induces cellular hyperplasia and, hence, is also implicated in cell cycle regulation. The homologue in monopartite begomoviruses (e.g. *Tomato leaf curl virus* (TLCV)) may play a similar role, although AC4 protein of bipartite begomoviruses appears to be functionally redundant. Curtovirus V2 protein influences the relative levels of ssDNA and dsDNA but its precise function is unknown.

Regulatory proteins

Rep binding to specific sequences within the begomovirus origin of replication interferes with complementary-sense transcription causing downregulation of its own expression. No evidence for such regulation has been shown for the mastreviruses, but RepA protein has been implicated in the stimulation of CP expression in these viruses. A similar function has been attributed to begomovirus AC2 (TrAP) protein, which transcriptionally transactivates CP and BV1 protein expression. Thus, these proteins provide a potential mechanism for a switch from early (complementary-sense) to late (virion-sense) gene expression, thereby enabling the synthesis of virus proteins at the appropriate time during the infection cycle.

Movement-associated proteins

The late gene products are required for virus movement and for encapsidation of viral DNA. Mastrevirus CP and begomovirus BV1 proteins function in nuclear trafficking of the viral DNA, and both are essential for systemic infection. Bipartite begomovirus CP is not essential for systemic infection in some hosts but may contribute to this process. Mastrevirus V1 and begomovirus BC1 are MPs required for cell-to-cell movement and are associated with plasmodesmata (e.g. MSV V1) or endoplasmic reticulum-derived tubules that extend across cell walls in infected tissue (e.g. *Squash leaf curl virus* (SqLCV) BC1). It is likely that nuclear and cell-to-cell movement is regulated by begomovirus BV1–BC1 and mastrevirus CP–MP interactions (Sanderfoot and Lazarowitz, 1996). Monopartite begomovirus V2 protein and curtovirus V3 protein also have been implicated in virus movement, and may compensate for the lack of a DNA B component.

Potential as virus vectors

Geminivirus DNA does not integrate into the host genome, but replicates episomally to a high copy number in the nucleus. Geminiviruses can thus be exploited to amplify foreign genes either by transfection of single cells,

tissue explants and whole plants or by stable transformation of plants (Stanley, 1993). Furthermore, they provide a source of regulatory sequences for crop transformation and molecular biological studies.

Transfection vectors

Begomoviruses such as ACMV and TGMV do not require CP for systemic infection and therefore the coding region may be replaced with heterologous genes to produce high levels of protein expression in systemically infected tissues. Since the CP is essential for insect transmission of the disease, its replacement reduces the risk of spread of engineered virus to other plants. However, only (approximately) genome-sized viral DNA is able to move within the plant, even in the absence of encapsidation, and this limits the size of the foreign gene insert. Transfection of single cells overcomes the need for cell-to-cell movement and results in stable replication of geminivirus vectors containing larger insertions. This tissue culture approach is necessary for high-level foreign gene expression from mastreviruses which need CP for systemic movement, and has been utilized with WDV replicons engineered as shuttle vectors able to replicate in both bacterial and plant cells. An alternative insertion site, the small intergenic region (SIR) (**Figure 1**), has been used to produce MSV vectors to study the excision of *Ac*/*Ds* elements.

Transformation vectors

An episomal vector can be produced in plants stably transformed with geminivirus DNA. When Rep protein is supplied *in trans*, either from the integrated DNA or the infecting cognate virus, integrated sequences flanked by copies of the origin of replication can be mobilized by homologous or replicative recombination events, and become amplified to high levels as an episomal vector. Foreign genes inserted into the viral DNA can thus be expressed at high levels. Unlike transfection vectors, the integrated viral DNA is a stable, heritable trait. Furthermore, as all cells contain a copy of the transgene, gene amplification throughout the plant does not depend on viral DNA movement, and so is not limited by the size constraints imposed on transfection vectors. This approach is suitable for all geminivirus genera.

Components for expression vectors

The detailed molecular analysis of geminivirus genomes has identified components of replication origins, promoters and *cis*- and *trans*-acting regulatory elements that modulate transcription and post-transcriptional processes. Such regulatory sequences are of growing use in areas of virology and pathology. For example, the knowledge that the begomovirus virion-sense promoter is induced by TrAP is being exploited specifically to amplify gene expression in infected cells in transgenic plants, and is being adapted to engineer resistance to geminivirus diseases. Sustained research, especially on replication and gene expression, promises a wealth of further opportunities and applications, including the ability to control gene expression temporally and in a tissue-specific manner.

Pathogenesis

The plant response to infection is manifested by the development of symptoms characteristic for a particular virus–host combination. The symptom phenotype is defined by complex interactions involving the environmental conditions, the morphology of the plant and its developmental stage at the time of infection. The genotype of the virus will influence its tissue tropism and accumulation. As a result of their genetic diversity and wide range of hosts, geminivirus diseases are associated with a variety of symptoms that include plant stunting, leaf curling and chlorosis, the production of enations (leaflets on the underside of infected leaves) and other tissue abnormalities (**Figure 3a**–**f**).

Chlorosis may be confined to the veins, as in *Ageratum yellow vein virus* (AYVV)-infected *Ageratum conyzoides* (**Figure 3c**), or it may sometimes produce spectacular mosaic symptoms, as seen in *Abutilon sellovianum* infected with AbMV (**Figure 3e**). Symptoms in *A. sellovianum* clearly affect tissues external to the phloem, yet AbMV is confined to the phloem. The virus may disrupt metabolite translocation within the phloem, thereby affecting the physiological state of neighbouring domains served, and delimited, by a network of minor veins.

Several geminivirus genes, particularly those involved in virus movement, have been identified as important pathogenic determinants. Mastreviruses produce characteristic chlorotic streak symptoms in members of the Poaceae family (**Figure 3a**). For MSV, host range and the timing and severity of symptoms are affected by changes in complementary-sense gene expression, which may affect both viral DNA replication (Rep protein) and virus movement (virion-sense gene expression stimulation by RepA). Streak width has been correlated with the expression of V1 protein and CP, both of which are essential for virus movement.

Curtoviruses produce characteristic symptoms of upward leaf roll and vein swelling on the lower surface of the leaf, a phenotype also associated with some monopartite begomoviruses such as TYLCV and AYVV (**Figure 3f**). Mutational analysis of BCTV has demonstrated that C4 protein is largely responsible for the phenotype. Expression of the protein in transgenic *Nicotiana benthamiana* induces tissue abnormalities that have been attributed to its function in the induction of cell division.

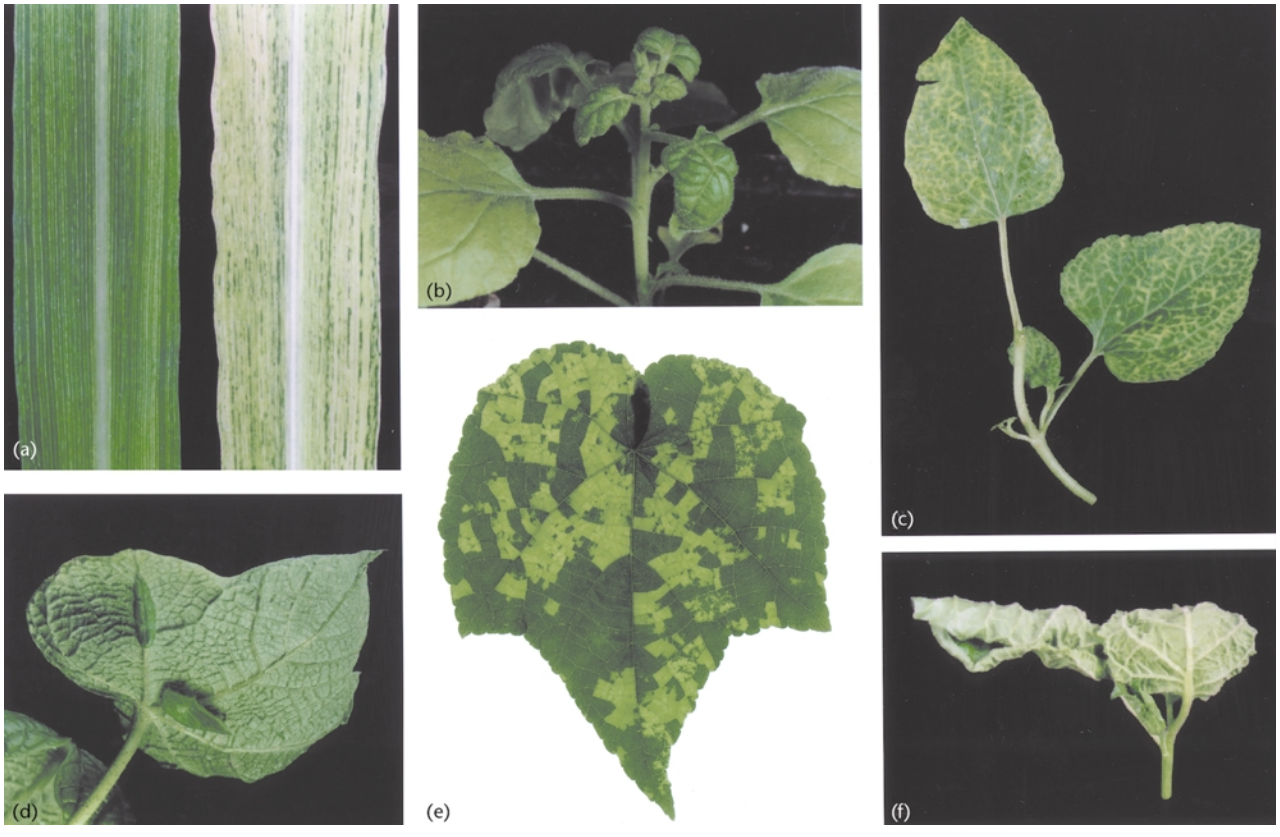

Figure 3 Geminivirus disease symptoms. (a) Mild and severe streak symptoms in MSV-infected maize. (b) Downward leaf curl in BeYDV-infected *N. benthamiana*. (c) Vein yellowing in AYVV-infected *Ageratum conyzoides*. (d) Virus-induced leaflets (enations) developing on the abaxial surface of CLCV-infected cotton. (e) Chlorotic mosaic in AbMV-infected *Abutilon sellovianum*. (f) Upward leaf roll and vein-swelling in AYVV-infected *N. benthamiana*, symptoms typical of many monopartite begomoviruses and curtoviruses.

Bipartite genome begomoviruses frequently produce downward leaf curl symptoms and chlorosis. Some, for example *Cotton leaf curl virus* (CLCV), induce enations (**Figure 3d**) although the virus genes responsible for this phenomenon have not yet been identified. The begomovirus movement protein (BC1) plays a significant role in pathogenesis. For example, differences in TGMV strain phenotypes have been mapped to altered amino acids within the BC1 protein, and expression of SqLCV BC1 protein in transgenic *N. benthamiana* and derivatives of tomato mottle virus (TMoV) BC1 protein in transgenic *N. tabacum* produce a phenotype reminiscent of virus-infected plants.

Transmission and Epidemiology

Transmission

All geminiviruses are transmitted in nature by insects (**Figure 4a**–**d**) in a persistent, circulative manner. With the exception of TPCTV, which is transmitted by the treehopper *Micrutalis malleifera* (family Membracidae), mastreviruses and curtoviruses are transmitted by leafhoppers (family Cicadellidae). Begomoviruses are transmitted by the whitefly *Bemisia tabaci* (family Aleyrodidae), although vegetative propagation of infected plants may result in the virus losing its ability to be insect-transmitted (e.g. AbMV in *A. sellovianum*). Transovarial transmission of TYLCV by *B. tabaci* has been reported, although geminiviruses appear not to replicate in insects. Geminiviruses are not transmitted through the seed or via pollen.

The transmission of MSV was studied in detail by Storey in the 1920s and 1930s. *Cicadulina mbila* is the most efficient vector. Transmission is a dominant sex-linked character with the male being heterozygous, which explains the higher transmission efficiency of females over males. Access to infected plants for only 15 s can result in sufficient MSV acquisition for transmission of the virus to healthy plants. The latent period required for the virus to circulate through the haemolymph and gain access to the salivary glands varies between 10 and 24 h.

Figure 4 Transmitting insects. (a) MSV vector *Cicadulina mbila*. (b) BCTV vector *Circulifer tenellus*. (c) TPCTV vector *Micrutalis malleifera*. (d) Begomovirus vector *Bemisia tabaci*.

The CP is essential for insect transmission and no other helper component has been identified. Thus, it is likely that the inability of *B. tabaci* to transmit AbMV during prolonged vegetative propagation of infected plants is a result of mutations occurring within the CP gene. Experiments using a chimaeric virus showed that the CP also determines insect specificity: when the CP coding region of ACMV was exchanged with that of BCTV, the virus was systemically infectious and produced geminate virus particles but, unlike ACMV, the chimaeric virus was transmitted by *Circulifer tenellus*, the insect that normally transmits BCTV.

Some geminiviruses can be introduced into plants by mechanical inoculation, although this is often an inefficient process. For example, ACMV is readily transmitted in this way to the experimental host *N. benthamiana*, but reintroduction into cassava requires biolistic delivery of the virus. BCTV cannot be introduced into sugarbeet by normal mechanical inoculation but can be inefficiently transmitted by stabbing a fine-gauge needle through virus inoculum into the crown of the plant. A similar technique may be used to inoculate germinating maize seeds with MSV. Efficient transmission of all members is possible using agro-inoculation, which involves plant inoculation with *Agrobacterium tumefaciens* containing partial or tandem repeats of the viral genome cloned into a T-DNA vector.

Epidemiology

Epidemiological studies of geminivirus diseases have focused on viruses and locations where significant crop losses occur (e.g. MSV and ACMV in Africa) and, more recently, on the wide range of begomoviruses that cause diseases in vegetables and fibre crops throughout Asia, the Americas and the Mediterranean Basin. Most of the diseases caused by these viruses are disseminated by insects, and consequently the epidemiology of the diseases is determined largely by insect biology and migratory behaviour. For ACMV an additional factor contributing to the spread of cassava mosaic disease is the use of infected cuttings for the vegetative propagation of cassava cultivars.

The incidence and severity of geminivirus diseases are affected by many epidemiological factors. For example, for MSV these include (1) differences in flight behaviour of leafhopper populations during different seasons, (2) the effect of late rainfall to favour the development of nymphs during the winter, (3) the preference of females for settling on streak-infected cereal plants, (4) the effect of the virus on fecundity of the females, (5) the importance of seedling age on the efficiency of virus infection, and (6) the effect of continual cereal cropping and planting downwind from previously planted cereal crops (Rose, 1978). Thus, changes in agricultural practices are responsible for the

increase in importance of the disease. This applies particularly to the planting and irrigation of cereal crops in the dry season, which provides a haven for insects and a reservoir for the virus. The optimization of planting practices and the use of resistant varieties are likely to remove the centres of the disease.

Similar factors affecting the dissemination of whitefly-transmitted diseases have been identified and studied in detail (Fauquet and Fargette, 1990), particularly in view of the recent emergence of the more aggressive B biotype of *B. tabaci* which has resulted in the rapid proliferation of many of these diseases (Brown, 1994).

Control

Control of geminivirus diseases using insecticides is ecologically unfavourable, and has been largely unsuccessful due to the need for frequent spraying. This is expensive and inevitably leads to insecticide resistance within insect populations. The use of protective nylon fleece is an effective but expensive alternative.

Despite extensive efforts, there has been only limited success in conventional breeding programmes to introgress resistance traits into agronomically important crops. There are a number of reports of severe infection of 'MSV-tolerant' maize, especially when the varieties are grown under environmental conditions different from those in which the plants were selected. Plants resulting from interspecific crosses between *Manihot esculenta* (cassava) and *M. glaziovii* show improved resistance to ACMV infection but none the less remain susceptible and are inherently less productive. Similarly, tomato plants produced by interspecific crosses between commercial varieties and resistant wild relatives such as *Lycopersicon chilense* and *L. peruvianum* remain susceptible to TYLCV infection. Little is known about the durability and effectiveness of such resistance against a broad range of geminiviruses. Recently, attention has focused on the use of genetic engineering as an alternative means to control geminivirus diseases, and a number of promising strategies are under development. Most work has targeted begomovirus diseases due to the recalcitrance of cereals to transformation.

Defective interfering DNA

Several geminiviruses are known to produce small, circular DNAs (**Figure 2b,c**) that have an adverse effect on virus proliferation and, hence, are referred to as defective interfering (DI) DNAs. *N. benthamiana* plants have been transformed with a tandem repeat of ACMV DI DNA. Following virus infection, extrachromosomal copies of DI DNA are mobilized and amplified to high levels at the expense of the genomic components, resulting in reduced virus accumulation and symptom amelioration. Similar results have been reported for BCTV DI DNAs. As this strategy relies on the ability of the infecting virus to replicate the DI DNA, plants show resistance only to closely related strains of virus from which the DI DNA is derived.

Antisense RNA

Antisense RNAs are usually targeted at the complementary-sense genes that not only are required early in the infection cycle but also are expressed from transcripts of relatively low abundance, giving a greater chance for success. Plants that are less susceptible to TYLCV (tomato and *N. benthamiana*), and TGMV (*N. tabacum*) infection have been produced by expressing Rep antisense RNA. The effectiveness of this approach against other geminiviruses depends on the level of homology between the target sequence and the antisense RNA.

Expression of virus proteins

The expression of geminivirus proteins or their derivatives in transgenic plants can confer resistance. For example, expression of TYLCV virion-sense genes or a truncated version of TYLCV Rep protein in tomato, and ACMV Rep protein in *N. benthamiana* resulted in plants that were less susceptible to infection by the homologous virus. The expression of TMoV defective MP (BC1) in transgenic *N. tabacum* has been shown to confer resistance to the virus. On this occasion, the degree of resistance correlated with the level of expression, suggesting that the defective protein functions as a dominant negative mutant of a movement function. The resistance was effective against *Cabbage leaf curl virus*, a distinct geminivirus, which suggests that this approach may result in broader spectrum resistance than strategies targeting viral DNA replication.

Virus-induced cell death

Begomovirus CP gene expression is induced by TrAP, and thus the expression of a transgene controlled from the CP promoter should be amplified specifically in virus-infected cells. Expression of a ribosome-inactivating protein (dianthin, a potent plant cytotoxin) from the ACMV virion-sense promoter conferred resistance to ACMV in transgenic *N. benthamiana* by rapidly killing infected cells and thereby containing the infection. Resistance was confined to ACMV isolates, implying that TrAP activity is virus-specific.

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