The Genetics and Genomics of Virus Resistance in Maize

12

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Abstract

Viruses cause significant diseases on maize worldwide. Intensive agronomic practices, changes in vector distribution, and the introduction of vectors and viruses into new areas can result in emerging disease problems. Because deployment of resistant hybrids and cultivars is considered to be both economically viable and environmentally sustainable, genes and quantitative trait loci for most economically important virus diseases have been identified. Examination of multiple studies indicates the importance of regions of maize chromosomes 2, 3, 6, and 10 in virus resistance. An understanding of the molecular basis of virus resistance in maize is beginning to emerge, and two genes conferring resistance to sugarcane mosaic virus, *Scmv1* and *Scmv2*, have been cloned and characterized. Recent studies provide hints of other pathways and genes critical to virus resistance in maize, but further work is required to determine the roles of these in virus susceptibility and resistance. This research will be facilitated by rapidly advancing technologies for functional analysis of genes in maize.

12.1 Introduction

Viruses cause significant disease in crops worldwide (Gomez et al. 2009; Kang et al. 2005), and they account for the majority of emerging diseases in plants (Anderson et al. 2004). In maize, losses due to virus diseases were estimated at 3% (Oerke and Dehne 2004). Based on estimated production of 875 million tonnes worldwide (Ranum et al. 2014), losses would be about 26 billion tonnes of grain valued at about 4.5 billion USD. Although more than 50 virus species can infect maize (Lapierre and Signoret 2004), only about a dozen of these cause significant disease problems (Stewart et al. 2016; Redinbaugh and Zambrano Mendoza 2014).

In contrast to most fungal and bacterial pathogens, viruses are obligate intracellular pathogens, dependent on the host cell for replication (Hull 2002). Plant virus genomes may

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consist of double-stranded or single-stranded RNA or DNA, may have a single genome segment or be multipartite, and generally encode fewer than 20 genes. Viruses generally enter plant cells due to mechanical disruption of the cell wall and membrane resulting from insect feeding, abrasion, or other means of wounding. Most maize-infecting viruses are transmitted by Hemipteran insects, but maize chlorotic mottle virus (MCMV) and wheat mosaic virus (WMoV, the causal agent of High Plains disease) are transmitted by thrips or beetles and mites, respectively (Cabanas et al. 2013; Nault et al. 1978; Stenger et al. 2016). Some viruses can also be transmitted through seed (Albrechtsen 2006), but well-documented rates of seed transmission are low for maize-infecting viruses (Johansen et al. 1994). In general, virus diseases occur when a source of virus and competent vectors occurs together with a susceptible host under suitable environmental conditions. Agronomic approaches to virus disease control include chemical control of insect vector populations, adjusting planting dates to avoid vectors, removal of weedy virus reservoirs and crop rotation. However, strong genetic resistance to most maize-infecting viruses has been identified, providing an economically sound, environmentally sustainable approach for disease control.

For the past 50 years, several viruses have caused, and continue to cause, significant agricultural problems in maize. Viruses in the family *Potyviridae*, primarily maize dwarf mosaic virus (MDMV) and sugarcane mosaic virus (SCMV), cause disease on maize everywhere the crop is grown (Stewart et al. 2016). Maize streak, caused by the geminivirus, maize streak virus (MSV), has been known for more than 100 years across sub-Saharan Africa, where it continues to cause significant food insecurity (Martin and Shepherd 2009). The rhabdovirus maize mosaic virus (MMV) was identified as a pathogen in 1960 (Herold et al. 1960), but the disease caused by the virus has been known for centuries in the tropics and sub-tropics where its planthopper vector is prevalent (Brewbaker 1979; Brewbaker 1981; Lapierre and Signoret 2004). The fijiviruses, maize rough dwarf virus (MRDV), and rice black-streaked dwarf virus (RBSDV), first emerged in Europe in the late 1940s (Lapierre and Signoret 2004). These viruses continue to cause crop losses there and in China, where agronomic practices facilitate large populations of viruliferous vectors. In South America, the related fijivirus, Mal de Rio Cuarto virus (MRCV) (Bonamico et al. 2010; Lapierre and Signoret 2004), also causes problems for farmers and seed producers. Disease caused by all of these viruses is controlled, at least to some extent, with resistant or tolerant maize hybrids and cultivars.

The recent emergence of two virus diseases is currently of concern. The most important is maize lethal necrosis (MLN), which results from the synergistic interaction of maize chlorotic mottle virus (MCMV) with another virus, usually from the family *Potyviridae* (Niblett and Claflin 1978). MLN was first described in the 10–70s in Kansas and Nebraska in the USA, where it caused significant but localized problems. Since 2011, however, MLN has rapidly emerged in sub-Saharan East Africa where it can cause up to 100% losses of maize crops (Mahuku et al. 2015; Wangai et al. 2012). MLN has also recently emerged and spread in China, Taiwan and Ecuador (Deng et al. 2014; Quito-Avila et al. 2016; Xie et al. 2011). Disease emergence has been closely tied to the presence of the MCMV vector, maize thrips (*Frankliniella williamsii* Hood), and to multiple annual maize crops (Cabanas et al. 2013; Mahuku et al. 2015). High Plains disease caused by WMoV was first discovered in the 1990s on maize in the US Midwest (Jensen et al. 1996). WMoV continues to cause important disease in wheat, and seed and sweet corn (Stewart et al. 2016). The disease causes problems for seed companies and maize breeders due to a potential for seed transmission (Jensen et al. 1996) that has led to phytosanitary restrictions to seed movement.

In model systems, we have some understanding of the molecular and genomic interactions among the host plant, viral pathogen, and insect vector that lead to virus susceptibility or resistance, but we are just beginning to define these events in cereal crops like maize.

12.2 Genome Sequencing for Virus Diagnostics and Characterization

Increasingly, next-generation sequencing (NGS) approaches are being used to identify viruses and characterize their populations in plants. Because most plant-infecting viruses have RNA genomes (and viruses with DNA genomes still make RNA transcripts), RNA-Seq approaches have been favored for these analyses. For maize, NGS was used to identify MCMV and SCMV in MLN-affected plants (Adams et al. 2013) and was subsequently used to demonstrate sequence homogeneity and diversity among MCMV and SCMV populations, respectively, in MLN-affected maize (Mahuku et al. 2015). NGS was also used to identify Johnsongrass mosaic virus (JGMV) in samples from Kenya and Uganda, and further experiments demonstrated a role for this virus in causing MLN (Stewart et al. 2017). A new polerovirus, tentatively named maize yellow mosaic virus, was identified in southwestern China using NGS (Chen et al. 2016) and was subsequently found in maize from southeastern China, Ecuador, and sub-Saharan Africa (Bernreiter et al. 2017; Palanga et al. 2017; Wang et al. 2016, Stewart et al. *unpublished results*). Similarly, a genome sequence related to fungal totiviruses was identified in maize (Chen et al. 2016). The clear utility of NGS for defining virus sequences and their diversity in crops indicates that this platform will become increasingly valuable as a diagnostic tool. However, the biological and epidemiological roles of the identified viruses must still be characterized to determine the role(s) of specific viruses identified by NGS in disease.

12.3 The Genetics of Virus Resistance in Maize

With few exceptions, maize inbred lines with strong virus resistance have been identified. In these lines, virus inoculation produces no or few symptoms. Importantly, the virus is excluded from or is found at significantly reduced titer in systemic plant tissues. An important exception to this is MCMV. For this virus, tolerant maize inbred lines developing few or no symptoms after inoculation with MCMV have been identified, but the virus is present at high titer in systemic tissues in these lines (Jones et al. 2018). Resistance has been associated with both dominant genes, such as those for resistance to potyviruses, and quantitative trait loci (QTL) with additive or dominant gene action, such as those for resistance to maize chlorotic dwarf virus (MCDV), maize rayado fino virus (MRCV), or maize mosaic virus (MMV) have been identified (Redinbaugh and Zambrano Mendoza 2014). Here again, MCMV is an exception, with a major QTL that have recessive character having been identified in two populations (Jones et al. 2018). Major QTL generally account for more than 20% of the phenotypic variation for resistance, although this is highly dependent on the population. Minor QTL, accounting for less than 10% of the phenotypic variance, have also been identified for resistance to several viruses.

12.3.1 Genetics of Potyvirus Resistance in Maize

Resistance to viruses in the *Potyviridae* has been investigated in US, European, Chinese, and tropical germplasm (reviewed in Redinbaugh and Pratt 2008; Pratt and Gordon 2006; Liu et al. 2009b). A strong correlation between MDMV and SCMV susceptibility was found among 122 European (Kuntze et al. 1997) and 155 U.S. and tropical (Jones et al. 2007) maize inbreds. Only three European lines (D21, D32, and FAP1360A) displayed complete resistance to SCMV and MDMV. The US line Pa405 and the Caribbean line Oh1VI are both completely resistant to MDMV, SCMV, and wheat streak mosaic virus (WSMV; Louie et al. 1991; Zambrano et al. 2014). Although minor gene resistance to these viruses has been identified in some lines, major loci for resistance have been identified in three genomic regions in all germplasm tested. Resistance to MDMV in Pa405 is conferred by a dominant resistance gene, *Mdm1*,

which mapped to the short arm of chromosome (chr.) 6 (McMullen and Louie 1989). Two or three genes involved in resistance to SCMV were identified in different crosses, and two dominant major resistance genes, *Scmv1* and *Scmv2*, were mapped on the short arm of chr. 6, and near the centromere of chr. 3, respectively (Melchinger et al. 1998). These resistance genes interact epistatically and are simultaneously required for expression of complete resistance to SCMV. *Scmv1* provides resistance at all developmental stages, and *Scmv2* is expressed at later stages of plant development (Xia et al. 1999). Pa405 carries three genes for resistance to WSMV: *Wsm1* on the short arm of chr. 6, *Wsm2* near the centromere of chr. 3, and *Wsm3* on the long arm of chr. 10 (McMullen et al. 1994). Thus, *Mdm1*, *Scmv1*, and *Wsm1* map to the same location, as do *Scmv2* and *Wsm2*.

In four separate studies, near-isogenic lines (NIL) carrying the *Scmv1* and *Scmv2*, or *Wsm1*, *Wsm2,* and *Wsm3* genes in various combinations, were tested for their responses to potyvirus species and isolates (Jones et al. 2011; Lubberstedt et al. 2006; Stewart et al. 2013; Xing et al. 2006) (Table 12.1). Inoculation of isogenic homozygous lines carrying resistance or susceptibility alleles derived from FAP1360A at *Scmv1* or *Scmv2* with the Seehausen isolate of SCMV (SCMV-Gr) and an Israeli isolate of MDMV (MDMV-MD) indicated that single gene was insufficient for resistance to either virus (Xing et al. 2006). The $F7^{RR/RR}$ line carrying both genes was completely resistant to SCMV-Gr, the Ohio isolate of MDMV (MDMV-OH), MDMV-MD, and the Ohio isolate of WSMV (WSMV-OH) (Lubberstedt et al. 2006). However, this line was susceptible to the Ohio SCMV

Table 12.1 Responses of lines carrying resistance loci on chromosomes 6, 3, and 10 to inoculation with potyvirus isolates[a]

			Chr[d]			*Virus isolate*[e]							
S recurrent parent	R source[b]	Line[c]	3	6	10	M-OH	M-It	M-MD	S-OH	S-Gr	J-Tx	Sr	W
F7	FAP1360A	$F7^{RR/RR}$	✓	✓		R[f]	S	R	S	R	–	–	R
		$F7^{RR/SS}$	✓			S	S	S	S	S	–	–	–
		$F7^{SS/RR}$		✓		R	S	S	S	V	–	–	–
		F7 control				S	S	S	S	S	–	–	S
Oh28	Pa405	$Oh28^{RR/RR/SS}$	✓	✓		R	R	–	R	R	R	R	R
		$Oh28^{SS/RR/RR}$		✓	✓	R	–	–	S	–	R	R	R
		$Oh28^{SS/RR/SS}$		✓		R	S	–	S	R	R	R	R
		$Oh28^{RR/SS/SS}$	✓			S	S	–	S	S	S	S	R
		$Oh28^{SS/SS/RR}$			✓	S	–	–	S	–	S	S	R
		Oh28 control				S	S	–	S	S	S	S	S

[a]The results presented are summarized from Jones et al. (2011), Lübberstedt et al. (2006), Stewart et al. (2013), Xing et al. (2006)

[b]The potyvirus resistant inbred line used as donor parent to generate near-isogenic lines. F7 and Oh28 were the potyvirus susceptible lines used as recurrent parents

[c]Near-isogenic lines (NIL) with resistance loci introgressed from the indicated resistance source. The superscripts xx/yy and xx/yy/zz indicate the presence of resistance (R) or susceptible (S) alleles on chr. 3 (x), 6 (y), and 10 (z)

[d]Chromsome; the check marks indicate the presence of resistance loci from chromosome 3, 6, or 10

[e]The virus isolate tested. *M-OH* maize dwarf mosaic virus (MDMV) Ohio isolate; *M-It* MDMV Italian isolate; *M-MD* MDMV Israel isolate; *S-OH* sugarcane mosaic virus (SCMV) Ohio isolate; *S-Gr* SCMV Seehausen isolate; *J-Tx* Johnsongrass mosaic virus Texas isolate; *Sr* sorghum mosaic virus Texas isolate; *W* WSMV Ohio isolate; *Wo* wheat mosaic virus Kansas isolate

[f]*R* resistant; *S* susceptible; *V* variable, expressing resistance at 7 dpi and susceptibility at 14 dpi; – not tested

isolate (SCMV-OH) and an aggressive isolate of MDMV from Italy (MDMV-It). Lines carrying *Scmv1* alone ($F7^{SS/RR}$) provided resistance to MDMV-OH and early resistance to SCMV-Gr, but the *Scmv2* gene alone ($F7^{RR/SS}$) did not provide any resistance. NIL carrying the *Wsm1* gene from Pa405 ($Oh28^{SS/RR/SS}$) were resistant to MDMV-OH and SCMV-Gr, but not MDMV-It or SCMV-OH. However, lines carrying both *Wsm1* and *Wsm2* ($Oh28^{RR/RR/SS}$) were resistant to all potyviruses tested. These results suggest that the Pa405-derived allele on chr. 6 (*Wsm1*) is stronger than the allele from FAP1360A (*Scmv1*). Although the patterns of resistance are similar for FAP1360A- and Pa405-derived isogenic lines, these two inbred lines are only distantly related (Xu et al. 2000).

Although NIL homozygous for *Wsm1* were completely resistant to MDMV-OH, epistatic resistance from *Wsm2* and *Wsm3*, or closely linked genes, was detected in NIL heterozygous for *Wsm1* (Jones et al. 2011). NIL carrying *Wsm1* were resistant to JGMV and sorghum mosaic virus (SrMV), and neither *Wsm2* nor *Wsm3* provided resistance on their own. Any of the three genes, *Wsm1, Wsm2,* or *Wsm3,* provided complete resistance to WSMV (McMullen et al. 1994). Together the results suggest that potyviruses and potyvirus isolates can vary in their virulence against the resistance genes on chr. 3 and 6, and indicate a relative virulence of (SCMV-OH ~ MDMV-It) > (SCMV-Gr ~ MDMV-OH ~ JGMV ~ SrMV) > WSMV. With the significant genomic sequence diversity among these viruses, it is of interest to identify the virus factors that influence virulence to determine whether conserved nucleotide or protein sequences, or conserved three-dimensional structures play roles in virus species and isolate virulence.

12.3.2 Resistance to Other Viruses in Other Families

In contrast to the potyviruses, which are easily mechanically transmitted under greenhouse and field conditions, many of the other important maize-infecting viruses must be transmitted using insect vectors, or more specialized techniques like agro-infiltration (Boulton et al. 1989) or vascular puncture inoculation (Louie 1995). Despite the difficulties associated with assessing phenotypic responses for obligately insect-vectored viruses, the genetics of resistance to at least eight virus diseases caused by potyviruses and eleven other virus species has been characterized (Redinbaugh and Zambrano Mendoza 2014). With our rapidly evolving resources for genotyping maize populations (Elshire et al. 2011; Ganal et al. 2011), genetic characterization of resistance has become limited only by our ability to develop populations and the ability to implement phenotypic analyses. Increasingly, genotyped association mapping populations, including the nested association mapping population, are available to researchers (Flint-Garcia et al. 2005; McMullen et al. 2009; Romay et al. 2013). These populations may prove invaluable for identifying virus resistance loci in maize, if a sufficient proportion of the population carries virus resistance.

Virus resistance loci have been found on nine of the ten maize chromosomes. By estimating the physical positions of markers for virus resistance QTL on the B73 v3 genome, results of previous studies were combined to identify nine clusters of virus resistance loci on chr. 1, 2, 3, 6, 8, and 10 (Table 12.2). While the same QTL for a given virus may have been identified in a number of studies (reviewed in Redinbaugh and Zambrano (2014), the positions of only the most well-defined QTL for each virus were included in Table 12.2.

Five of the resistance QTL are associated with a single virus, and three of these are for resistance to maize streak virus (MSV), which is the only DNA virus currently causing disease problems in maize. These are found in bins 1.06, 2.06, and 3.09 (Nair et al. 2015; Welz et al. 1998). The other two individual QTL are for tolerance to MCMV and resistance to maize stripe virus (Dintinger et al. 2005; Jones et al. 2018). One of the resistance locus clusters (chr. 8) includes only QTL for two highly related fijiviruses in the family *Reoviridae*, suggesting this locus might also be unique.

Table 12.2 Overlapping virus resistance loci in maize

Chr[a]	Bin	Midpoint (Mb)[b]	Range (Mb)	Virus[c]	Family[d]	References
1	1.03	52.1 ± 3.2	41.1–67.7	MMV	*Rhabdoviridae*	Zambrano et al. (2014)
				MRCV	*Reoviridae*	DiRenzo et al. (2004)
2	2.02	60.6 ± 5.6	8.0–199.9	MRCV	*Reoviridae*	Martin et al. (2010)
				RBSDV	*Reoviridae*	Luan et al. (2012)
				MSpV	*Phenuiviridae*	Dinterger et al. (2005)
				MCMV	*Tombusviridae*	Jones et al. (2018)
	2.08	222.3 ± 5.1	211.2–231.5	MFSV	*Rhabdoviridae*	Zambrano et al. (2014)
				MMV	*Rhabdoviridae*	Zambrano et al. (2014)
				MSpV	*Phenuiviridae*	Dinterger et al. (2005)
3	3.05	122.5 ± 22.7	56.8–161.2	WSMV	*Potyviridae*	McMullen et al. (1994)
				SCMV	*Potyviridae*	Ding et al. (2012)
				MDMV	*Potyviridae*	Zambrano et al. (2014)
				MMV	*Rhabdoviridae*	Ming et al. (1998)
				MSpV	*Phenuiviridae*	Dintinger et al. (2005)
				WoMV	*Fimoviridae*	Lubberstedt et al. (2006)
				MSV	*Geminiviridae*	Welz et al. (1998)
				MCDV	*Secoviridae*	Jones et al. (2004)
4	4.08	212 ± 28.8	187.5–246.9	MRCV	*Reoviridae*	Bonamico et al. (2012)
				MSV	*Geminiviridae*	Welz et al. (1998)
				MCDV	*Secoviridae*	Jones et al. (2004)
6	6.01	27.3 ± 10.4	8.3–71.2	WSMV	*Potyviridae*	McMullen et al. (1994)
				MDMV	*Potyviridae*	Zambrano et al. (2014)
				SCMV	*Potyviridae*	Liu et al. (2017)
				MCDV	*Secoviridae*	Zambrano et al. (2014)
				WMoV	*Fimoviridae*	Lubberstedt et al. (2006)
				MFSV	*Rhabdoviridae*	Zambrano et al. (2014)
				MMV	*Rhabdoviridae*	Zambrano et al. (2014)
	6.05	153.5 ± 4.0	148–157	MSV	*Geminiviridae*	Pernet et al. (1999)
				MCMV	*Tombusviridae*	Jones et al. (2018)
8	8.07	173.1	168.6–173.1	RBSDV	*Reoviridae*	Luan et al. (2012)
				MRCV	*Reoviridae*	Bonamico et al. (2012)
10	10.05	130.4 ± 8.6	86.4–137.5	MRFV	*Tymoviridae*	Zambrano et al. (2014)
				MNeSV	*Tombusviridae*	Zambrano (2013)
				MCMV	*Tombusviridae*	Jones et al. (2018)
				BYDV	*Potyviridae*	Horn et al. (2015)
				WSMV	*Potyviridae*	McMullen et al. (1994)
				MDMV	*Potyviridae*	Zambrano et al. (2014)
				SCMV	*Potyviridae*	Zhang et al. (2013)
				MCDV	*Secoviridae*	Jones et al. (2004)
				MSV	*Geminiviridae*	Pernet et al. (1999)
				MSpV	*Phenuiviridae*	Dintinger et al. (2005)

[a]*Chr* chromosome
[b]Physical position in the B73 v3 genome
[c]*MMV* maize mosaic virus; *MRCV* Mal de Rio Cuarto virus; *RBSDV* rice black-streaked dwarf virus; *MSpV* maize stripe virus; *MCMV* maize chlorotic mottle virus; *MFSV* maize fine streak virus; *WSMV* wheat streak mosaic virus; *SCMV* sugarcane mosaic virus; *MDMV* maize dwarf mosaic virus; *WMoV* wheat mosaic virus; *MSV* maize streak virus; *MCDV* maize chlorotic dwarf virus; *MRFV* maize rayado fino virus; *MNeSV* maize necrotic streak virus
[d]*Family* the virus family

The major clusters of virus resistance loci include the regions of the potyvirus resistance clusters on chr. 3, 6, and 10 (Redinbaugh and Zambrano Mendoza 2014). These regions also carry loci for resistance to several fungal pathogens (Wisser et al. 2006) (Table 12.2). In addition to potyviruses, these clusters encode resistance to 5, 4, and 7 other viruses, respectively. Two clusters of virus resistance genes are present on chr. 2. One, in bin 2.02, includes QTL for resistance to three viruses in two different families (Di Renzo et al. 2004; Jones et al. 2018; Luan et al. 2012; Martin et al. 2010; Zambrano et al. 2014). In the other, overlapping QTL provides resistance for the rhabdoviruses MMV and MFSV and the tenuivirus MSpV (Dintinger et al. 2005; Zambrano et al. 2014). Similarly, clusters on chr. 4 and 6 (bin 6.05) confer resistance to two or three viruses in different virus families. The virus species within each cluster have little or no sequence identity, have different tissue specificities, and employ different replication and translation strategies.

Germplasm carrying strong resistance to one group of viruses in these clusters is not necessarily resistant to other types of viruses. For example, inbred line Pa405 is strongly resistant to potyviruses and WMoV; however, it is highly susceptible to a number of other viruses for which resistance loci are present on chr. 3, 6, and 10 including MCDV, MMV, MFSV, MNeSV, and MRFV. Because most resistant inbred lines used in these mapping studies carry resistance to a limited range of virus families, it seems likely that single loci are not responsible for providing resistance to all viruses within a cluster.

The inbred line Oh1VI was developed from an open-pollinated Virgin Island population as highly resistant to MCDV (Louie et al. 2002) and was subsequently found to be highly resistant to MDMV, SCMV, and WSMV (Jones et al. 2007). Further study indicated the line is highly resistant to MRFV, MMV, MFSV, and MNeSV and somewhat tolerant of MCMV (Zambrano et al. 2013; Mahuku et al. 2015; Jones et al. 2018). The virus resistance present in Oh1V1 was mapped to the same clusters previously identified in comparisons of mapping studies using diverse maize germplasm (Fig. 12.1). Further studies to fine-map virus resistance in these clusters in Oh1VI are ongoing. The results of these studies could provide opportunities to examine roles for a "birth and death" model, in which individual genes in multigene families are created by gene duplication and may later become inactivated or deleted from the genome, for virus resistance genes (Nei and Rooney 2005) or to identify unique mechanisms for virus resistance (Gomez et al. 2009).

12.4 Virus Resistance Genes in Maize

12.4.1 *Scmv1*

Following the identification of major resistance loci, *Scmv1* and *Scmv2*, tremendous efforts have been made to fine-map the two genes with mapping populations derived from the European

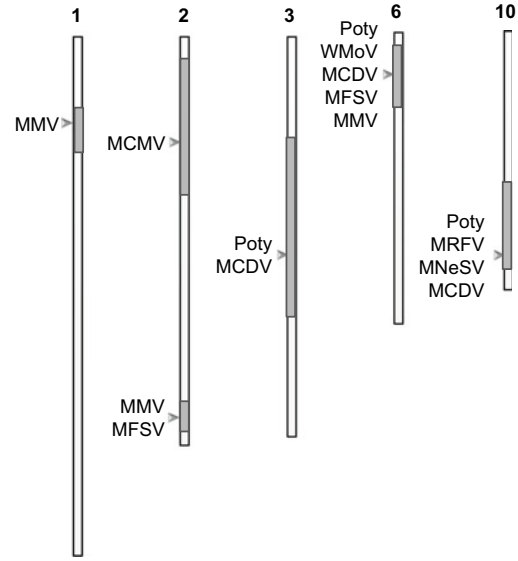

Fig. 12.1 Virus resistance in maize inbred line Oh1VI. The physical positions of markers associated with Oh1VI virus resistance QTL were determined by comparison to the B73 genome of research published. The positions of six gene clusters on five maize chromosomes are indicated by grey bars. The triangles indicate the mean position for identified QTL peaks. Potyvirus includes maize dwarf mosaic virus, sugarcane mosaic virus, and wheat streak mosaic virus

cross FAP1360A × F7 (Xu et al. 1999; Dussle et al. 2003; Yuan et al. 2004; Ingvardsen et al. 2010), Chinese maize inbred lines (Lü et al. 2008; Zhang et al. 2003), and tropical germplasm (Wu et al. 2007). Linkage mapping with three segregating populations finally assigned *Scmv1* to a 59.21 kb region of chr 6 containing three predicted genes (Tao et al. 2013). Candidate gene-based association mapping revealed that *ZmTrxH*, encoding an atypical h-type thioredoxin, was most likely to be the candidate for *Scmv1* (Tao et al. 2013; Leng et al. 2015). Inbred lines lacking the resistant allele of *ZmTrxH* were highly susceptible to SCMV. *ZmTrxH* was validated as *Scmv1* through a transgenic complementation assay, and *ZmTrxH* transcript abundance was demonstrated to be closely associated with resistance to SCMV. Intriguingly, *ZmTrxH* alleles from both resistant and susceptible lines shared identical coding/proximal promoter regions, but varied in their upstream regulatory regions. In contrast to more than 30 other thioredoxins encoded by the maize genome, *ZmTrxH* has an atypical WNQPS structure within the thioredoxin active-site motif, in which the two canonical cysteines found in the other thioredoxins are replaced by asparagine (N) and serine (S) in both the resistant and susceptible alleles (Liu et al. 2017). This change renders *ZmTrxH* unable to reduce disulfide bridges, the typical activity of thioredoxins; however, the *ZmTrxH* protein has a strong molecular chaperone-like activity. Thioredoxins have previously been implicated in virus infection and resistance, with the silencing of a maize m-type thioredoxin enhancing systemic infection of SCMV (Shi et al. 2011). In addition, overexpression of a *Nicotiana benthamaniana* h-type thioredoxin conferred resistance to tobacco mosaic virus and cucumber mosaic virus, two (+)-strand RNA viruses from different families (Sun et al. 2010). *ZmTrxH* is dispersed in the cytoplasm and suppresses viral accumulation without eliciting the SA- or JA-mediated pathogen defense signaling pathway associated with R-gene-mediated resistance (Liu et al. 2017). These results shed new insight into plant viral defense mechanisms and define a process which is obviously different from that conferred by NB-LRR-type R genes.

12.4.2 *Scmv2*

Using a large isogenic mapping population, *Scmv2* was mapped to an interval of 1.34 Mb on chr 3, covering four predicted genes possibly involved in virus movement (Ingvardsen et al. 2010). Later, *Scmv2* was fine-mapped to an interval of 196.5 kb with two predicted genes, encoding an auxin-binding protein (ABP1) and a Rho GTPase-activating protein, as candidate genes for *Scmv2* (Ding et al. 2012). Candidate gene-based association mapping revealed a significantly associated marker 207FG003 in the *Scmv2* region (Leng et al. 2015). Combined genome-wide association study (GWAS) and linkage analyses revealed four genes at *Scmv2*, and one of them, encoding *ABP1*, was the most likely candidate for *Scmv2* (Li et al. 2016). The native *ABP1* gene, including 1.7 kb of the promoter region and 1 kb downstream of the coding region, was isolated from the resistant line FAP1360A and used for functional complementation assay (Leng et al. 2017). Susceptible genotypes at the *Scmv2* locus were complemented by transgenic full-length *ABP1* to confer resistance, while downregulation of *ABP1* by RNAi resulted in susceptible plants. Sequence variation in the *ABP1* promoter region resulted in higher expression that was associated with SCMV resistance. The ABP1 protein has no effect on SCMV replication, but it most likely confines systemic viral infection by directly interacting with Rubisco small subunit (RbCS) (Leng et al. 2017). Thus, the well-characterized gene *ABP1* confers resistance to a potyvirus in plants.

Previous studies have implicated interactions between the chloroplast and viral proteins in the development of disease. In particular, interactions between potyvirus coat proteins and chloroplast components have been identified (reviewed in Zhao et al. 2016). The RbCS protein has been implicated in resistance to tomato mosaic virus conferred by the *Tm-2*^{2} gene

product, which interacts with the viral movement protein to prevent systemic virus movement (Zhao et al. 2013).

12.4.3 Other Potential Virus Resistance Genes

Recessive virus resistance genes in plants have previously been associated with mutations in translation factors (Robaglia and Caranta 2006), and recessive alleles of eIF4e confer virus resistance in several hosts (Diaz-Pendon et al. 2004; Gomez et al. 2009). In this resistance mechanism, the protein produced from the recessive allele fails to interact with the virus and recruit the viral RNA to cap-binding complex. In addition, eIF4e has been shown to move from cell to cell, with some alleles of eIF4e preventing cell-to-cell movement of the potyvirus, pea seed-borne mosaic virus (Gao et al. 2004). Within the larger genome region of chr. 3 that carries QTL for resistance to MCDV, MMV, and MRFV in the multi-virus-resistant inbred line Oh1VI, the B73 genome encodes two genes for the translation factor eIF4e (Zambrano et al. 2014). However, these eIF4e genes are not within the *Scmv2* regions identified in fine-mapping studies (Ding et al. 2012; Ingvardsen et al. 2010; Leng et al. 2017). The recessive character of the MCMV tolerance QTL that mapped to chr 6 in maize inbreds KS23-5 and KS23-6 could be associated with a translation factor. Genes encoding elongation factor 1 alpha (eEF1A) are present on chr 6. In several plant virus systems, eEF1A interact with viral replicases and are thought to recruit viral RNAs to the replication complex (Sanfacon 2015). Further research is needed to determine whether translation factors play any role in virus resistance in maize.

Although other virus resistance genes remain to be identified from maize, pathogen-derived resistance in transgenic maize expressing viral RNAs derived from MCDV, SCMV, and MSV has resistance to these viruses (Liu et al. 2009a; McMullen et al. 1996; Shepherd et al. 2007; Shepherd et al. 2014; Zhang et al. 2013). In addition, maize expressing an *E. coli* ribonuclease specific for double-stranded RNA had increased resistance to RBSDV (Cao et al. 2013).

12.5 Genomic and Transcriptomic Responses to Viruses in Maize

Information on the responses of susceptible and resistant maize to virus inoculation is accumulating. In dicots, inoculation with viruses has been shown to increase cellular stress and defense gene expression, alter expression of genes regulating development and hormone responses, and increase expression of genes involved in RNAi (reviewed in Whitham et al. 2006). For maize, the transcriptomic and proteomic responses of resistant and susceptible plants to infection with SCMV, MDMV, and RBSDV have been studied. Despite the differences in these viruses—the potyvirus (SCMV and MDMV) genomes are monopartite, single-stranded, positive sense RNA, and the RBSDV genome is multipartite, enveloped, double-stranded RNA—there are common themes in the responses of susceptible and resistant maize. Similar to dicots, increased levels of defense genes were noted in maize inoculated with potyviruses or RBSDV up to 9 and at 50-day post-inoculation, respectively (Cassone et al. 2014; Jia et al. 2012; Li et al. 2011; Shi et al. 2006; Uzarowska et al. 2009; Wu et al. 2013a; Zhou et al. 2016). However, differences in both specific transcripts/proteins that accumulated and the timing of their accumulation were noted between resistant and susceptible maize inbreds, with the responses generally being of greater magnitude and/or faster in resistant plants. Other virus-related changes included expression of genes associated with carbohydrate and energy metabolism, protein degradation, signal transduction, hormone synthesis and response, and cell wall development.

Transcripts of genes with functions in RNA interference (RNAi), the pathways used by many organisms to regulate gene expression and virus infections, accumulated in both RBSDV- and

SCMV-inoculated maize. In experiments to characterize siRNA associated with RBSDV infection, inoculation of susceptible maize resulted in accumulation of gene-specific transcripts for dicer (*Dcl1*, *2, 3a*), argonaute (*Ago1a, 1b2, 18a*) and RNA-dependent RNA polymerase (*Rdr6*) (Li et al. 2017). Experiments to characterize siRNA in susceptible maize after SCMV inoculation revealed upregulation of *Dcl2* and *Ago2*, but downregulation of *Dcl4* (Xia et al. 2014). *Dcl2* accumulated in susceptible maize inoculated with SCMV, MCMV or both viruses (MLN), with significantly higher levels of transcript in MLN-inoculated plants, but expression of other *Dcl* genes was either not affected or reduced by virus inoculation (Xia et al. 2016). In this system, *Ago2A* and *Ago18a* accumulated in virus inoculated plants, with patterns similar to *Dcl2*. In contrast, the highest levels of *Ago1a*, *1b*, and *1c* transcripts were found in SCMV-inoculated plants (Li et al. 2017). In Arabidopsis, *Ago2* and *Dcl2* are required to control viral infections caused by adapted viruses (Zhang et al. 2012). Although the roles of specific *Dcl* and *Ago* genes have not been defined in maize, *Dcl2* appears to be required for efficient intercellular movement of the virus-induced gene silencing (VIGS) signal in *N. benthamiana* (Qin et al. 2017). While at least some members of the *Dcl*, *Ago* and *Rdr* families co-localize with the observed clusters of virus resistance loci in maize, the relationship between these genes and resistance is not known.

Increased expression of transcripts for genes important for photosynthesis has been noted in some systems. For example, the large subunit of RuBisCO accumulated in resistant maize inoculated with SCMV (Wu et al. 2013a; Wu et al. 2015). Chloroplast localized ferredoxin V and thioredoxins was also upregulated (Cao et al. 2012; Cheng et al. 2008; Wu et al. 2015). Taken together with interactions of SCMV viral proteins with the RuBisCo small subunit and ferredoxin (Cheng et al. 2008; Leng et al. 2017), the results suggest an intimate relationship between photosynthetic activity and potyvirus infection.

It is perhaps not surprising that similar regulation of only a very limited number of specific genes or proteins was identified in the experiments outlined above, because of differences in the viruses, germplasm (including the presence or absence of resistance), time after inoculation and even the tissues analyzed. Among the common threads were increased accumulation of β-glucanase transcripts in plants inoculated with either SCMV or MDMV, with higher levels in resistant lines (Cassone et al. 2014; Shi et al. 2006; Uzarowska et al. 2009). Increased accumulation of transcripts with similarity to brassinosteroid-insensitive receptor kinase, a gene with roles in innate immunity and plant growth, occurred in virus-resistant plants inoculated with MDMV and RBSDV (Cassone et al. 2014; Huot et al. 2014; Jia et al. 2012). Remorin genes were upregulated in resistant and susceptible MDMV-inoculated plants Cassone et al. 2014, and susceptible SCMV-inoculated plants (Wu et al. 2013b). Remorin proteins are located within punctate membrane microdomains and have been implicated in virus spread in plants (Konrad and Ott 2015; Raffaele et al. 2009). While none of these genes has been associated with a specific virus resistance QTL, the similar regulation of genes provides a basis for development of studies to examine the roles of specific genes and pathways in virus resistance and susceptibility in maize.

Changes in the expression of specific genes have been associated with virus resistance in maize. As noted above, 100-fold higher expression of the *Scmv1/ZmTrxH* gene was associated with the resistance response in line FAP1360A relative to susceptible controls (Liu et al. 2017). Interestingly, an m-type thioredoxin mapping to chr. 5 was also upregulated in maize inoculated with SCMV, and silencing of its expression inhibited SCMV accumulation in maize and tobacco vein-banding virus in tobacco (Shi et al. 2011). Cao et al. (2012) showed that a Rho-related GTPase induced during SCMV infection of susceptible plants is required for virus infection. Rop genes have been shown to regulate pathogen resistance including virus resistance (Sacco et al. 2007; Zhang et al. 2014) and have been implicated in abscisic acid responses, development and stress responses

(Craddock et al. 2012). Elongin C, a transcription factor that increases transcription elongation by RNA polymerase II, interacts with the potyviral genomic protein and is expressed at higher levels at 4–6 days post-inoculation (Zhu et al. 2014). In addition, the SCMV HC-Pro interacts with the transit peptide of the chloroplastic ferredoxin V, and expression of this gene is downregulated during SCMV infection (Cheng et al. 2008). The exact roles of these proteins in enhancing or suppressing virus infection and their association with QTL for virus resistance remain to be determined.

12.6 Conclusions

Improvements in phenotyping plants for virus resistance, genotyping maize populations, and functional analysis of candidate genes are likely to accelerate increased understanding of genes, proteins, and mechanisms associated with virus resistance in maize. The recent identification of the genes underlying *Scmv1* and *Scmv2* provides the basis for understanding whether potyvirus resistance, and resistance to other viruses, is pleiotropic in maize. Characterization of these genes will also aid in our understanding of the mechanisms some isolates use to break resistance that is critical to understanding the durability of alleles deployed to control the disease. Our ability to edit plant genomes will facilitate validation of the importance of candidate genes in virus resistance and should aid in the development of highly productive, disease-resistant maize crops.

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