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Review

Solanum resistance genes against *Phytophthora infestans* and their corresponding avirulence genes

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SUMMARY

Resistance genes against *Phytophthora infestans* (*Rpi* genes), the most important potato pathogen, are still highly valued in the breeding of *Solanum* spp. for enhanced resistance. The *Rpi* genes hitherto explored are localized most often in clusters, which are similar between the diverse *Solanum* genomes. Their distribution is not independent of late maturity traits. This review provides a summary of the most recent important revelations on the genomic position and cloning of *Rpi* genes, and the structure, associations, mode of action and activity spectrum of Rpi and corresponding avirulence (Avr) proteins. Practical implications for research into and application of *Rpi* genes are deduced and combined with an outlook on approaches to address remaining issues and interesting questions. It is evident that the potential of *Rpi* genes has not been exploited fully.

INTRODUCTION

The cultivation of potato and other solanaceous species, such as tomato, still suffers from quantitative and qualitative losses caused by the late blight pathogen *Phytophthora infestans*, incurring enormous costs for disease prevention. Among the various taxonomic, climatic and geographical variables, the taxonomic level of the host species, and thus the genetic composition of the host, has been identified as the best predictor for the late blight resistance of *Solanum* spp. (Spooner *et al*., 2009). The improvement of commercial potato and tomato cultivars by resistance breeding is considered to represent a meaningful contribution to the reduction of yield losses caused by late blight. Potato breeding is complicated by polyploidy, heterozygosity, crossing barriers, linkage drag and high-quality trait demands (Gebhardt, 2004; Jacobsen and Schouten, 2007; van der Vossen *et al*., 2003). Although quantitative resistance, as found in *S. tuberosum* ssp. *andigenum*, *S. berthaultii* and *S. vernei* (Andrivon *et al*., 2003), *S. verrucosum* (Rivera-Peña, 1990), *S. microdontum* (Sandbrink *et al*., 2000) and *S. paucissectum* (Villamon *et al*., 2005), appears to be more durable (Colon *et al*., 1995a, b), combining quantitative trait loci (QTLs) for resistance with other desirable traits is more demanding and time consuming in comparison with introducing monogenic resistance. In addition, strong association of partial late blight resistance with late foliage maturity is well documented (Collins *et al*., 1999; Salaman, 1910; Toxopeus, 1958). Resistance genes against *Phytophthora infestans* (*Rpi* genes) are easier to introduce than QTLs, and those that have either been mapped in or cloned from *Solanum* spp. are listed in Table 1. However, the *Rpi* gene content of numerous wild *Solanum* spp. still remains untested (Jacobs *et al*., 2010), and their resistance has been clarified only partially. Sources of resistance have been reported predominantly in the tuber-bearing species of the section *Petota*, and mainly originate from North, Central and South America.

Although *R1*–*R4* were described in 1953 as the first *Rpi* genes (Black *et al*., 1953) and numerous other *Rpi* genes have been discovered since, the investigation of their mechanistic mode of action and their exploitation in resistance breeding have only made significant progress since the 2000s. *R1*, *R3*, *R2*, *R4* and *R10* of *S. demissum* have been introgressed into cultivated potato stepwise (van der Lee *et al*., 2001; Park *et al*., 2009b; van der Vossen *et al*., 2005), but were quickly overcome in the field (Müller, 1951; Toxopeus, 1956). *Phytophthora infestans* isolates collected before its second worldwide migration, starting from Mexico in 1984 (Goodwin and Drenth, 1997), are genetically highly similar (Drenth *et al*., 1993, 1994; Fry *et al*., 1992). In contrast, the complex race structure of most *P. infestans* populations today (Rauscher *et al*., 2006, Swiezyński *et al*., 2000) and the prevalence of both A1 and A2 mating types (GILB, 1999) limit the benefit of the introduction of single race-specific major resistance genes (Drenth *et al*., 1994). Defeated *R* genes, however, may still be conducive to late blight resistance (Pedersen and Leath, 1988; Stewart *et al*., 2003), a possible result of fitness costs arising from the maintenance of virulence factors by the pathogen (Montarry *et al*., 2010). Currently, a major strategy is to search for and integrate genes that confer broad-spectrum resistance to late blight (Park *et al*., 2009a, b), such as *Rpi-blb1* (allelic to *RB*), *Rpi-blb2* and *Rpi-blb3* (Park *et al*., 2005a; Song *et al*., 2003; van der Vossen *et al*., 2003, 2005) from the Mexican wild species *S. bulbocastanum* Dunal. ($2n = 2x = 24$) (Hermsen and Boer, 1971), and *Rpi-blb1* homologues *Rpi-sto1* and *Rpi-pta1* from the

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Table 1 Mapped and/or cloned *Solanum* spp. *Rpi* (resistance genes against *Phytophthora infestans*) genes**.**

R gene	Class	Chromosome	Original species	References
Rpi-avl1		XI^{d}	*avilesii*	Ruiz de Galarreta *et al*. (1998), Verzaux (2010)
Rpi-ber, *Rber*		X^{a}	*berthaultii*	Colon *et al*. (1995a, b), Rauscher *et al*. (2006), Tan *et al*. (2010)
Rpi-ber1		X^{a}	*berthaultii*	Colon *et al*. (1995a, b), Park *et al*. (2009a)
Rpi-ber2		X^{a}	*berthaultii*	Colon *et al*. (1995a, b), Park *et al*. (2009a)
Rpi-blb1, *RB*	CC-NB-LRR	VIII^{a}	*bulbocastanum*	Bhaskar *et al*. (2008, 2009), Bradeen *et al*. (2009), Iorizzo *et al*. (2011), Liu and Halterman (2009), Millett *et al*. (2009), Naess *et al*. (2000), Song *et al*. (2003), Vleeshouwers *et al*. (2008), van der Vossen *et al*. (2003, 2005), Wang *et al*. (2008)
Rpi-blb2	CC-NB-LRR	VI^{a}	*bulbocastanum*	van der Vossen *et al*. (2005)
Rpi-blb3	CC-NB-LRR	IV^{a}	*bulbocastanum*	Lokossou *et al*. (2009), Park *et al*. (2005a)
Rpi-abpt	CC-NB-LRR	IV^{a}	*bulbocastanum*	Lokossou *et al*. (2009), Park *et al*. (2005a, b)
Rpi-bt1		VIII	*bulbocastanum*	Oosumi *et al*. (2009)
Rpi-cap1		XI^{d}	*capsicibaccatum*	Jacobs *et al*. (2010), Verzaux (2010)
(*Rpi-blb1*, *-blb2*, *-blb3*)			*cardiophyllum*	Lokossou *et al*. (2010)
Rpi-crp1		IX^{a}	*caripense*	Nakitandwe (2007), Trognitz and Trognitz (2005)
Rpi-qum1		XI^{d}	*circaeifolium*	Morante and Villanueva (2006), Verzaux (2010)
R1	CC-NB-LRR	V^{a}	*demissum*	Ballvora *et al*. (2002), Eschen-Lippold *et al*. (2010), Gebhardt and Valkonen (2001), Kuang *et al*. (2005), Meksem *et al*. (1995)
R2	CC-NB-LRR	IV^{a}	*demissum*	Li *et al*. (1998), Lokossou *et al*. (2009), Park *et al*. (2005a, b)
R3a	CC-NB-LRR	XI^{b}	*demissum*	El-Kharbotly *et al*., (1996), Huang (2005), Huang *et al*. (2004, 2005)
R3b	CC-NB-LRR	XI^{a}	*demissum*	El-Kharbotly *et al*. (1996), Huang (2005), Huang *et al*. (2004), Li *et al*. (2011)
R4^{Bl}			*demissum*	van Poppel (2010), van Poppel *et al*. (2009b)
R4^{Ma}		XII?	*demissum*	van Poppel (2010), van Poppel *et al*. (2009a, b)
R5		XI^{a}	*demissum*	Huang (2005)
R6		XI^{a}	*demissum*	El-Kharbotly *et al*. (1996), Huang (2005)
R7		XI^{a}	*demissum*	El-Kharbotly *et al*. (1996), Huang (2005)
R8	NB-LRR	IX^{a}	*demissum*	Huang (2005), Jo *et al*. (2011)
R9		XI^{a}	*demissum*	Huang (2005)
R10		XI^{a}	*demissum*	Bradshaw *et al*. (2006), Huang (2005)
R11		XI^{a}	*demissum*	Bradshaw *et al*. (2006), Huang (2005)
Rpi-demf1		IV^{a}	*demissum*	Danan *et al*. (2011), Hein *et al*. (2007)
Rpi-dlc1		IX^{a}	*dulcamara*	Golas *et al*. (2010)
Rpi-dlc2		X^{a}	*dulcamara*	Golas *et al*. (2010, 2012)
Rpi-edn1.1	NB-LRR	IV^{a}	*edinense*	Champouret (2010), Lokossou *et al*. (2009)
Rpi-edn1.2		IV^{a}	*edinense*	Champouret (2010), Lokossou *et al*. (2009)
Rpi-edn2		IX^{a}	*edinense*	Verzaux (2010)
Rpi-edn3		XI	*edinense*	Verzaux (2010)
Rpi-hjt1.1	NB-LRR	IV^{a}	*hjertingii*	Champouret (2010), Lokossou *et al*. (2010)
Rpi-hjt1.2	NB-LRR	IV^{a}	*hjertingii*	Champouret (2010), Lokossou *et al*. (2010)
Rpi-hjt1.3	NB-LRR	IV^{a}	*hjertingii*	Champouret (2010), Lokossou *et al*. (2010)
Ph-1, *Ph*		VII	*lycopersicum*	Peirce (1971)
Rpi-mch1		VII	*michoacanum*	Sliwka *et al*. (2012b)
Rpi-mcd1		IV^{a}	*microdontum*	Colon *et al*. (1995b), Lokossou (2010), Sandbrink *et al*. (2000), Tan *et al*. (2008)
Rpi-mcq1, *Rpi-moc1*		IX^{c}	*mochiquense*	Jones *et al*. (2010), Nowicki *et al*. (2012), Smilde *et al*. (2005)
(*Rpi-blb3*)			*nayaritense*	Lokossou *et al*. (2010)
Rpi-oka1			*okadae*	Jones *et al*. (2010), Nowicki *et al*. (2012)
Rpi-pcs		XI^{a}	*paucissectum*	Villamon *et al*. (2005)
Rpi-phu1	CC-NB-LRR	IX^{b}	*phureja*	Sliwka *et al*. (2006, 2010)
Ph-2		X^{a}	*pimpinellifolium*	Laterrot (1975)), Moreau *et al*. (1998), Turkensteen (1973
Ph-3		IX	*pimpinellifolium*	Chunwongse *et al*. (2002), Park *et al*. (2010), Truong *et al*. (2013)
Ph-5-1		I	*pimpinellifolium*	Merk and Foolad (2012), Nowicki *et al*. (2012)
Ph-5-2		X	*pimpinellifolium*	Merk and Foolad (2012), Nowicki *et al*. (2012)
Rpi1		VII	*pinnatisectum*	Kuhl *et al*. (2001), Lokossou *et al*. (2010)
Rpi-pur1		XI^{d}	*piurae*	Rietman (2011)
Rpi-rzc1		X^{a}	*ruiz-ceballosii*	Sliwka *et al*. (2012a)
Rpi-snk1.1	NB-LRR	IV^{a}	*schenckii*	Champouret (2010), Jacobs *et al*. (2010)
Rpi-snk1.2	NB-LRR	IV^{a}	*schenckii*	Champouret (2010), Jacobs *et al*. (2010)
(*Rpi-blb1*, *-blb3*)			*stenophyllidum*	Lokossou *et al*. (2010)
Rpi-bst1			*stenophyllidum*	Hein *et al*. (2009)
Rpi-sto1	NB-LRR	VIII^{a}	*stoloniferum*	Vleeshouwers *et al*. (2008), Wang *et al*. (2008)
Rpi-sto2	CC-NB-LRR	XI^{a}	*stoloniferum*	Champouret (2010)
Rpi-pta1	NB-LRR	VIII^{a}	*stoloniferum*	Vleeshouwers *et al*. (2008), Wang *et al*. (2008)
Rpi-pta2			*stoloniferum*	Vleeshouwers *et al*. (2008), Wang *et al*. (2008)
Rpi-plt1		VIII^{a}	*stoloniferum*	Wang *et al*. (2008)
Rpi-Smira1		XI?	*tuberosum* cv. Sarpo Mira	Rietman (2012)
Rpi-Smira2			*tuberosum* cv. Sarpo Mira	Rietman (2012)
Rpi-vnt1.1, *Rpi-phu1*	CC-NB-LRR	IX^{a}	*venturii*	Foster *et al*. (2009), Pel *et al*. (2009)
Rpi-vnt1.2	CC-NB-LRR	IX^{a}	*venturii*	Foster *et al*. (2009)
Rpi-vnt1.3	CC-NB-LRR	IX^{a}	*venturii*	Foster *et al*. (2009), Pel *et al*. (2009)
Rpi-vnt2		XI^{d}	*venturii*	Rietman (2011)
Rpi-ver1	NB	VI^{a}	*verrucosum*	Jacobs *et al*. (2010), Liu and Halterman (2006), Wang *et al*. (2008)
R2-like	CC-NB-LRR	IV^{a}	-unknown-.	Lokossou *et al*. (2009), Park *et al*. (2005a, c)

Right to the *R* genes pseudonyms are listed respective protein class, chromosomal location, specific origin and a selection of references. Genes highlighted in grey have been cloned already. Upper case letters a, b, or c subsequent to the chromosomal location mark *R* gene groups with similar chromosomal location.
CC, coiled coil; LRR, leucine-rich repeat; NB, nucleotide binding.

tetraploid Central American species *S. stoloniferum* (Vleeshouwers *et al*., 2008; Wang *et al*., 2008). In contrast with other *Rpi* genes, *Rpi-blb1* and *Rpi-blb2* conferred stable resistance in diverse trials over several years, as demonstrated by slowed lesion development and reduced sporulation (Lozoya-Saldana *et al*., 2005; Millett and Bradeen, 2007; Song *et al*., 2003; van der Vossen *et al*., 2003, 2005). Given that *IpiO1* and *IpiO2* presumably cause *Avr-blb1* activity in the majority of European and North American *P. infestans* isolates analysed to date (Vleeshouwers *et al*., 2008), the introduction of *Rpi-blb1*, *Rpi-sto1* or *Rpi-pta1* could result in broad late blight resistance. The germplasm of *S. bulbocastanum* (Park *et al*., 2005a; Ramanna and Hermsen, 1971), *S. stoloniferum* (Hutten and van Berloo, 2001, referred to as sto or CPC 2093) and *S. microdontum* has been exploited in the breeding of numerous cultivars. *Solanum microdontum Rpi-mcd1* confers broad-spectrum late blight resistance of foliage, delaying infection in the field for 3–11 days on average (Tan *et al*., 2008, 2010), and evidence indicates that the resistance extends to the tuber (Park *et al*., 2005d). As only one isolate of a larger collection sampled in Poland between 1999 and 2008 was capable of overcoming *S. phureja Rpi-phu1*, it has been assumed that this gene could also contribute significantly to durable late blight resistance when introgressed into commercial cultivars together with other *Rpi* genes (Foster *et al*., 2009). As an alternative to classical breeding, molecular cloning and the transfer of resistance genes, such as *Rpi-blb1* and *Rpi-blb2*, into cultivar Fortuna (Dixelius *et al*., 2012) is less time-consuming, avoids linkage drag and overcomes crossing barriers (Park *et al*., 2009b). However, genetic engineering of crops currently suffers from a considerable lack of appreciation by consumers in several countries (http://www.gmo-compass.org) and is an expensive process.

Classically, pathogen recognition receptors (PRRs), which monitor conserved pathogen-associated molecular patterns (PAMPs) to initiate PAMP-triggered immunity (PTI), have been discerned from *R*-gene products, which monitor rather specific effectors to initiate effector-triggered immunity (ETI) (reviews by Göhre and Robatzek, 2008; Hein *et al*., 2009; Jones and Dangl, 2006; Zipfel 2008, 2009). A continuum between PTI and ETI, instead of clear dichotomy, has however been suggested, as some PAMPs show little evolutionary conservation, contribute to virulence and/or elicit a strong hypersensitive response (HR) (Thomma *et al*., 2011). In addition, there is evidence that many mechanisms and molecular components of resistance are shared among PRR- and *R*-gene-mediated resistance in plants (reviews by Dangl and Jones, 2001; Deslandes and Rivas, 2011; Ingle *et al*., 2006; Nürnberger *et al*., 2004). The gene-for-gene hypothesis implies that the product of an *R* gene recognizes a specific avirulence (*Avr*) gene product of the pathogen (Flor, 1971; Keen, 1990). This interaction model has, however, been refined subsequently, as direct physical interaction has been observed only in rare experimental settings, e.g. for dicot nucleotide-binding leucine-rich repeat (NB-LRR) protein–Avr protein combinations of flax protein L and AvrL567 from *Melampsora lini* (Dodds *et al*., 2006), *Arabidopsis* RRS1-R and PopP2 from *Ralstonia solanacearum* (Deslandes *et al*., 2003), tobacco N and the p50 helicase domain of *Tobacco mosaic virus* (TMV) (Ueda *et al*., 2006), and potato RB and IPI-O1/IPI-O4 from *P. infestans* (Chen *et al*., 2012). Two advanced models have been developed according to which the R protein perceives modifications of an additional host factor. According to the 'guard model', pathogen effectors target and modify functional guardees (van der Biezen and Jones, 1998b; Dangl and Jones, 2001), whereas the 'decoy model' hypothesizes the targeting of decoy proteins that act exclusively in effector recognition (van der Hoorn and Kamoun, 2008).

This review summarizes current knowledge on *Solanum Rpi* genes (*SRpigs*), Rpi proteins (SRpips), their Avr counterparts and molecular interactions, and intends to support further research and its application by highlighting aspects not yet elucidated and by listing methodical advice. We present a 'developmental bottleneck' model, which may explain the decrease in late blight resistance at late developmental stages, even occurring in cultivars harbouring *Rpi* genes.

EFFECTORS AND Avr PROTEINS—STRUCTURE AND FUNCTION

Effectors may be defined as molecules which are secreted by plant-associated organisms and alter host cell structure and function (Hogenhout *et al*., 2009). *Avr* genes, which are present in plant-pathogenic viruses, bacteria, fungi, oomycetes, nematodes and insects, encode effectors which are recognized and cause ETI of the host, in contrast with virulence genes (Luderer and Joosten, 2001; Skamnioti and Ridout, 2005; White *et al*., 2000). Depending on whether their site of action is extracellular or within the host symplast, apoplastic and cytoplasmic effectors are discerned. During infection, *P. infestans* induces and secretes both apoplastic and cytoplasmic effectors (Damasceno *et al*., 2008; Haas *et al*., 2009; Tian *et al*., 2007; Whisson *et al*., 2007). Apoplastic effectors may either protect the pathogen against host defences or mediate its invasion (Wawra *et al*., 2012a). Some apoplastic effectors of *P. infestans* inhibit host proteases (Song *et al*., 2009; Tian *et al*., 2004, 2005, 2007) or glucanases (Damasceno *et al*., 2008), whereas others putatively hydrolyse glycosylates (McLeod *et al*., 2003) or disrupt cell wall–plasma membrane adhesion by association with lectin receptor kinases (Gouget *et al*., 2006; Senchou *et al*., 2004). Many genes encoding cytoplasmic effectors have been found within the genome of *P. infestans* strain T30-4, including 563 genes belonging to the RXLR and 196 genes belonging to the Crinkler (CRN) family (Haas *et al*., 2009). Both of these consist of modular proteins comprising an N-terminal signal peptide, an N-terminal and a C-terminal domain, which, in several cases, are functional in secretion, translocation into host cells and effector activity, respectively (Haas *et al*., 2009, Morgan and Kamoun, 2007; Schornack *et al*., 2010, Fig. 1).

To date, all experimentally verified *P. infestans Avr* genes encode RXLR effectors (Boyd *et al*., 2012; Jiang *et al*., 2008). However, the putative transcription factor pi3.4 has also been suggested as an origin of incompatibility to R3b and R10 (Qutob *et al*., 2006), in addition to RXLR effectors (Rietman, 2011). The large, highly diverse RXLR superfamily is named after the first of two conserved tetrameric sequence motifs in the N-terminal half, following the signal peptide (Haas *et al*., 2009, Jiang *et al*., 2008; Rehmany *et al*., 2005; Whisson *et al*., 2007). The RXLR domain of Avr3a has been shown to mediate homodimerization (Bos *et al*., 2010). As several RXLR effectors comprise nuclear localization signals (NLSs), it has been suggested that they may partially manipulate host gene expression (Morgan and Kamoun, 2007). Within the C-terminal half or effector domain, four more motifs have been identified: the K motif (Dou *et al*., 2008a) and motifs W, Y and L (Jiang *et al*., 2008). Stretches similar to the 49-residue WY domain motif, consisting of a W motif, a loop and a Y motif, have been found in 44% of annotated RXLR effectors from *P. infestans*, *P. ramorum* and *P. sojae* (Boutemy *et al*., 2011). There has been a controversial debate about the occurrence and molecular site of phosphatidylinositol-3-phosphate (PI(3)P) binding and its role for effector entry, both in general and for Avr1b in particular. Diverse recent findings have indicated a multitude of specific PI(3)P-binding affinities for different subgroups of effectors from filamentous pathogens: some effectors bind PI(3)P with the RXLR(-like) domain (Bhattacharjee *et al*., 2012a, b; Kale *et al*., 2010; Plett *et al*., 2011), others with their C-terminal part (Gan *et al*., 2010; Wawra *et al*., 2012b; Yaeno *et al*., 2011), or with both domains (Sun *et al*., 2013), or do not bind to PI(3)P at all (Gan *et al*., 2010; Yaeno *et al*., 2011). NMR analysis of AVR3a4 and structure modelling revealed a conserved, positively charged patch within the effector domain, which probably mediates PI(3)P binding of 1b3a subfamily effectors (Sun *et al*., 2013; Yaeno *et al*., 2011). Tertiary structure analysis revealed an α-helical fold conserved in 44% of annotated *Phytophthora* RXLR effectors (Boutemy *et al*., 2011), and will be key to the understanding of further structure–function relationships within other effector subfamilies.

Rpi GENE-ENCODED PROTEINS—STRUCTURE AND FUNCTION

R genes, which account for approximately 1%–3% of the genome of potato, rice and poplar (Andolfo *et al*., 2013; Kohler *et al*., 2008; Potato Genome Sequencing Consortium, 2011), have been assigned to four classes (van Ooijen *et al*., 2007; Table 2).

Intracellular NB-LRR proteins constitute two of these classes: TIR-NB-LRR (TNL) proteins, which are rare in monocots (Tarr and Alexander, 2009), but represent a major fraction in dicots (Bakker *et al*., 2011; Kohler *et al*., 2008), have an N-terminal conserved

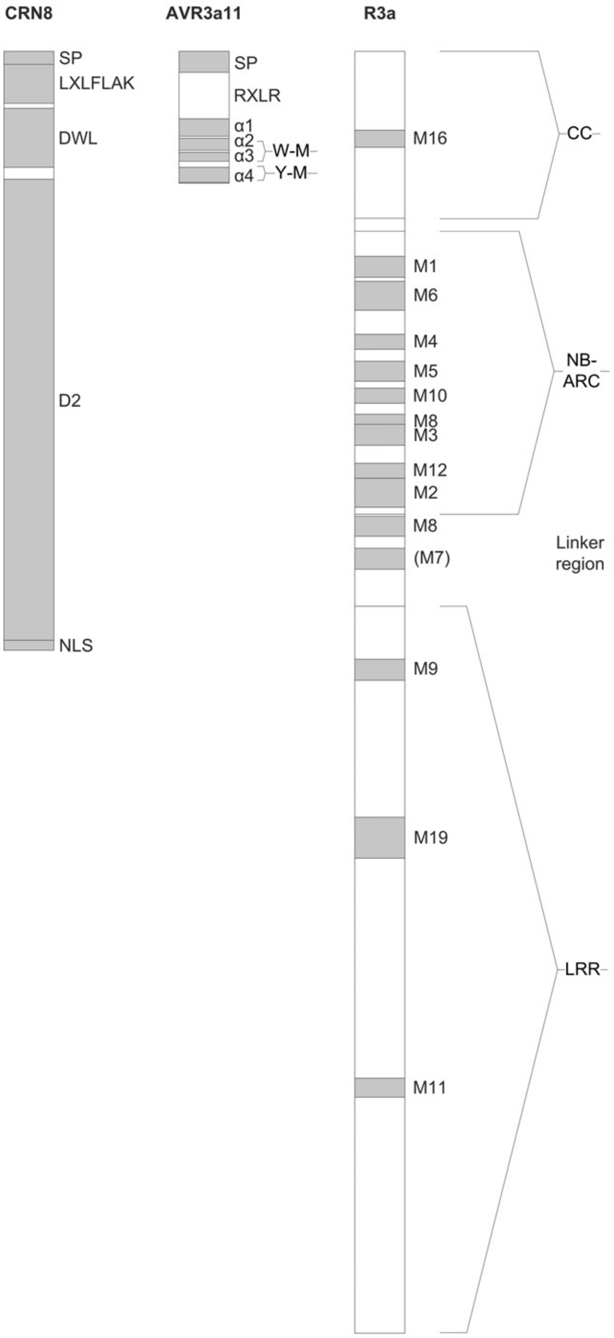

Fig. 1 Modular structure of effectors: *Phytophthora infestans* CRN8 and *P. capsici* Avr3a11, and *Solanum demissum* R3a. Structural elements: SP, signal peptide; LXLFLAK, LXLFLAK domain; DWL, DWL domain; D2, D2 domain; NLS, nuclear localization signal; RXLR, RXLR domain; α1–α4, helices α1–α4; W-M, W-M motif; Y-M, Y-M motif; CC, coiled coil domain; NB-ARC, NB-ARC domain; linker region; LRR, LRR domain; M1–M19, motifs 1–19, corresponding to: M16, EDxxD; M1, P loop; M6, RNBS-A; M4, Kin-2; M5, RNBS-B; M10, RNBS-C; M2, RNBS-D, M9, LDL; In contrast with the other motifs, M7 did not align well to R3a (only 19% compared with, otherwise, at least 34% amino acid identity). References: Boutemy *et al*. (2011), van Damme *et al*. (2012), Huang *et al*. (2005) and Jupe *et al*. (2012).

Table 2 *R*-gene classes of solanaceous plants.

	Solanum lycopersicum	*Solanum tuberosum*
CNL	93 (0.268%)	163 (0.466%)
TNL	18 (0.052%)	43 (0.123%)
RLP	176 (0.507%)	403 (1.151%)
RLK	261 (0.752%)	301 (0.86%)
Others	198 (0.57%)	421 (1.203%)

CC, coiled coil; CNL, CC-NB-LRR; LRR, leucine-rich repeat; NB, nucleotide binding; RLK, receptor-like kinase; RLP, receptor-like protein; TIR, *Drosophila* Toll and mammalian interleukin-1 receptor; TNL, TIR-NB-LRR.

Number and percentage of candidate resistance genes (Andolfo *et al*., 2013).

domain that resembles the *Drosophila* Toll and mammalian interleukin (IL)-1 receptor (TIR) domain. Proteins of the second class, CC-NB-LRR (CNL), often contain an N-terminal coiled-coil (CC) structure, occasionally in the form of a leucine zipper region (Hammond-Kosack and Jones, 1997; Martin *et al*., 2003; Pan *et al*., 2000). Recently, the first crystal structure of the CC domain of a CNL revealed a helix–loop–helix structure (Maekawa *et al*., 2011). This domain supported dimerization to tightly packed rod-shaped homodimers and presumably supports interaction with other proteins (Lupas, 1996; Maekawa *et al*., 2011). As opposed to short CC domains, extended CC domains which contain the Solanaceae domain (SD) have exclusively been reported to date for Solanaceae (Lukasik-Shreepaathy *et al*., 2012, Mucyn *et al*., 2006). Additional predicted CC domains within the N-terminus (Hwang and Williamson, 2003; van der Vossen *et al*., 2005) and highly conserved tryptophan residues within both block II and block III of the NB site (Pan *et al*., 2000) have been recognized as further sequence characteristics specific to these CNL proteins with an extended CC domain. Many plant CNLs also contain a non-TIR (nT) motif of the form EDxxD, which presumably is involved in intramolecular interaction (van Ooijen *et al*., 2007). To date, all determined *SRpigs* encode proteins of the CNL class (Table 1).

As NB-LRRs commonly lack predicted transmembrane segments or signal peptides, they probably reside and perceive *Avr* products in the cytoplasm (Boyes *et al*., 1998; van der Vossen *et al*., 2003). As a result of the prediction of four myristoylation and 43 phosphorylation sites for R1, its putative anchoring in the plasma membrane and participation in signal transduction by (de-)phosphorylation steps have been suggested (Ballvora *et al*., 2002).

Several reports suggest that CNLs and TNLs to some extent require different downstream signalling components, indicating involvement of the N-terminus in downstream signalling: In different plant families, TNL based resistance is strongly dependent on enhanced disease susceptibility 1 (EDS 1) (Gassmann *et al*., 1999; Liu *et al*., 2002a; Parker *et al*., 1996; Shirano *et al*., 2002), whereas a large fraction of CNLs studied to date seem to mainly depend on nonrace-specific disease resistance (NDR1) (Aarts *et al*., 1998; Tornero *et al*., 2002, review by Martin *et al*., 2003).

The NB domain occurring in APAF-1, certain *R*-gene products and CED-4 (NB-ARC domain; van der Biezen and Jones, 1998a) binds and hydrolyses ATP, but is also important for overall functionality of the *R*-gene product (Tameling *et al*., 2002; Ueda *et al*., 2006; Walker *et al*., 1982). In plants, the NB-ARC domain consists of the three subdomains NB, ARC1 and ARC2 (reviewed by Albrecht and Takken, 2006). In analogy with ADP-bound APAF-1, these could form a compact globular NB pocket consisting of a five-stranded parallel β sheet surrounded by seven α-helices, a helix bundle or a winged helix fold (van Ooijen *et al*., 2007; Riedl *et al*., 2005; Takken and Goverse, 2012). It is assumed that the NB domain functions as a molecular switch, inducing a conformational change by NTP hydrolysis to regulate signal transduction (Leipe *et al*., 2004). The NB-ARC domain contains eight highly conserved motifs, of which motifs RNBS-A and RNBS-D differ substantially in TIR- and non-TIR-NB-LRRs (Jupe *et al*., 2012; Meyers *et al*., 2003), and the P loop of the NB site is assumed to be involved in resistance signalling through interaction with the CC or TIR domains (Belkhadir *et al*., 2004; Moffett *et al*., 2002).

LRR domains are involved in protein–protein interaction and ligand recognition in all domains of life and also in viruses (Enkhbayar *et al*., 2004). For CNL, steric structures of LRR domains have been proposed based on related proteins (Takken and Goverse, 2012). LRR domains comprise 2–42 repeats, which, in plants, are formed by 24–28 residues including a 14-residue core of the pattern LxxLxxLxLxxC/Nxx adopting a β-sheet structure and adjacent loop regions (van Ooijen *et al*., 2007). In addition to a conserved VLDL motif in the third repeat, which could possibly function as a nuclear export signal (La Cour *et al*., 2004), LRRs contain two subdomains common to both TNLs and CNLs (Jupe *et al*., 2012, Fig. 1). In plant R proteins, the LRR domain is considered to be a main determinant in pathogen recognition specificity (Dodds *et al*., 2001; Ellis *et al*., 1999; Rairdan and Moffett, 2006), and to function directly (Ellis *et al*., 2007; Jia *et al*., 2000; Ueda *et al*., 2006) or indirectly (Burch-Smith *et al*., 2007; Lokossou, 2010, review by Innes, 2004) in the binding of *Avr* gene products. Intramolecular interaction of the LRR domain with other regions has been shown for tobacco N (Ueda *et al*., 2006) and for bell pepper Bs2 *in vitro* (Leister *et al*., 2005), and has been suggested for R2 (Lokossou, 2010). The LRR domain generally seems to interact with the ARC1 subdomain, whereas the ARC2 subdomain has been suggested to relay pathogen recognition at the LRR domain into conformational changes, leading to downstream signalling. It is assumed that the entire LRR domain is necessary for activation on interaction with the CC-NB-ARC part (Rairdan and Moffett, 2006). Mutations disrupting such inter- or intramolecular interactions functioning in the negative regulation of defence responses have been shown to result in the constitutive activation of defence responses and lethality (Bendahmane *et al*., 2002; Hwang and Williamson, 2003; Shirano *et al*., 2002; Zhang *et al*., 2003). The LRR region is the most variable segment in closely related NB-LRR proteins and its β-strand/β-turn motif has been shown to be under divergent selection in *Solanum* spp. (Parniske *et al*., 1997; van der Vossen *et al*., 2000) and other species (Ellis *et al*., 1999; McDowell *et al*., 1998; Meyers *et al*., 1998). In contrast with NB-LRR proteins, R proteins of the remaining two classes are predicted to contain an N-terminal extracellular LRR (eLRR) domain. Attached to the eLRR domain by a transmembrane domain, their cytoplasmic part either contains a protein kinase domain (receptor-like kinases or RLKs) or does not (receptor-like proteins or RLPs) (van Ooijen *et al*., 2007). Several R proteins and many candidates do not fit into any of these four classes, and therefore were occasionally assigned to distinct further R-protein classes (Martin *et al*., 2003). For evolutionary aspects, we refer to Andolfo *et al*. (2013), Couch *et al*. (2006), Kuang *et al*. (2005) and Wang *et al*. (2008).

GENOMIC LOCATION OF *Rpi* GENES

Nonrandom, uneven distribution within specific genomes of the Solanaceae and other plant families (Young, 2000) has been shown for *R* genes (Gebhardt and Valkonen, 2001; Jacobs *et al*., 2010) and resistance gene analogues (RGAs) (Andolfo *et al*., 2013; Bakker *et al*., 2003, 2011), giving rise to clusters and hot spots of *R* genes that confer resistance to unrelated, but also similar, antagonists. Within the potato genome draft sequence, 728 RGAs have been mapped to 47 different loci (15.5 RGA/region on average; Bakker *et al*., 2011). Currently, 60 of the 68 known *SRpigs* have been mapped, and are dispersed on 16 regions on 10 chromosomes (3.75 *Rpi*/region; Table 1).

R-gene clustering may enhance the shuffling of sequence polymorphism through unequal inter- and intragenic meiotic recombination, leading to duplication, partial deletion or the reassembly of genes, thereby generating new *R*-gene specificities, partially from pseudogenes (Hulbert *et al*., 2001). The genomic distribution of *R* genes in the solanaceous species tomato, potato and pepper is not independent, but often corresponds to each other (Andolfo *et al*., 2013; Grube *et al*., 2000), enabling the homology-based identification of *Rpi* genes (Huang *et al*., 2005). Some authors have suggested that quantitative resistance to late blight could be a side-effect of maturity traits with a possible contribution of residual effects of succumbed *R* genes (Tan *et al*., 2008; Allefs *et al*., 2005). Indeed, a potato QTL meta-analysis revealed the overlapping and juxtaposition of many meta-QTLs for late blight resistance and maturity, but also clearly distinct QTLs and meta-QTLs, indicating that pleiotropic or closely linked genes could exist in addition to unlinked genes underlying these two traits (Danan *et al*., 2011).

The distribution of *Solanum Rpi* genes and RGAs has been found to be significantly independent of the distribution of late blight resistance meta-QTLs. Artificial separation as a result of as yet undetected QTLs, or artificial clustering caused by insufficient resolution, however, cannot be excluded.

Interestingly, the genomic location of *Solanum* RGAs and *Rpi* genes does not seem to be independent of the location of maturity traits. The number of RGAs and *SRpigs* located in maturity meta-QTLs is significantly higher than expected (Danan *et al*., 2011). Furthermore, the analysis of maturity classes of potato cultivars (http://www.europotato.org) and information on the presence of *SRpigs* (http://www.euroblight.net) revealed a significant delay in the maturity of 205 cultivars which harbour *SRpigs*, compared with 547 cultivars lacking *SRpigs* (J. Rodewald & B. Trognitz, unpublished results; Table 4).

Interestingly, pathogen infection may also result in epigenomic and genomic alterations at *R* clusters, e.g. hypomethylation and rearrangement, as has been shown for *Nicotiana tabacum* (Boyko *et al*., 2007).

Rpi GENE EXPRESSION

Comparatively few studies on *SRpigs* have addressed the expression of functional *R* genes. To fulfil a role as cellular sentinels, R proteins must be present in plant cells prior to attack, and therefore *R* genes are assumed to be constitutively expressed (Iorizzo *et al*., 2011). The transcription of *R3a* (Huang *et al*., 2005), *RB* (Song *et al*., 2003) and *Hero* (Poch *et al*., 2006) has indeed been observed in unchallenged leaves of *S. tuberosum*, *S. bulbocastanum* and *S. lycopersicum*, respectively. Although some *R* genes, such as tomato *Bs4*, tomato *Mi-1.2* and potato *R3a*, seem to remain transcribed at steady-state levels (Goggin *et al*., 2004; Huang *et al*., 2005; Schornack *et al*., 2005), it has been shown that some *Solanum* resistance gene homologue (RGH) or *Rpi* genes, such as *RB*, are induced on late blight infection in *Solanum* spp. (Henriquez and Daayf, 2010; Kramer *et al*., 2009; J. Rodewald & B. Trognitz, unpublished results), as is the case for the *N. tabacum R* gene *N* following TMV infection (Levy *et al*., 2004). The presence of some *SRpig*-related expressed sequence tags only in pathogen-challenged libraries (Ronning *et al*., 2003) could also result from pathogen-triggered induction of at least some RGHs. There is also evidence for tissue-specific transcript levels of *R* genes or RGHs (Brugmans *et al*., 2008). Some RGAs are referred to as pseudogenes owing to premature stop codons, frameshift indels or large deletions, but are nevertheless expressed (Paal *et al*., 2004). *RB* transcript levels were roughly consistent throughout the developmental stages of pre-flowering, post-flowering and near-senescence in *RB*-transformed *S. tuberosum* cv. Dark Red Norland, and therefore it is unlikely that the decrease in late blight resistance observed at increasing physiological age of potato plants is caused by changes in the expression of the *RB* transgene (Millett *et al*., 2009). Similar transcript levels of *RB* within two *RB* transgenic potato lines at flowering, 2 weeks and 4 weeks after flowering, irrespective of the environmental temperature (10, 20 or

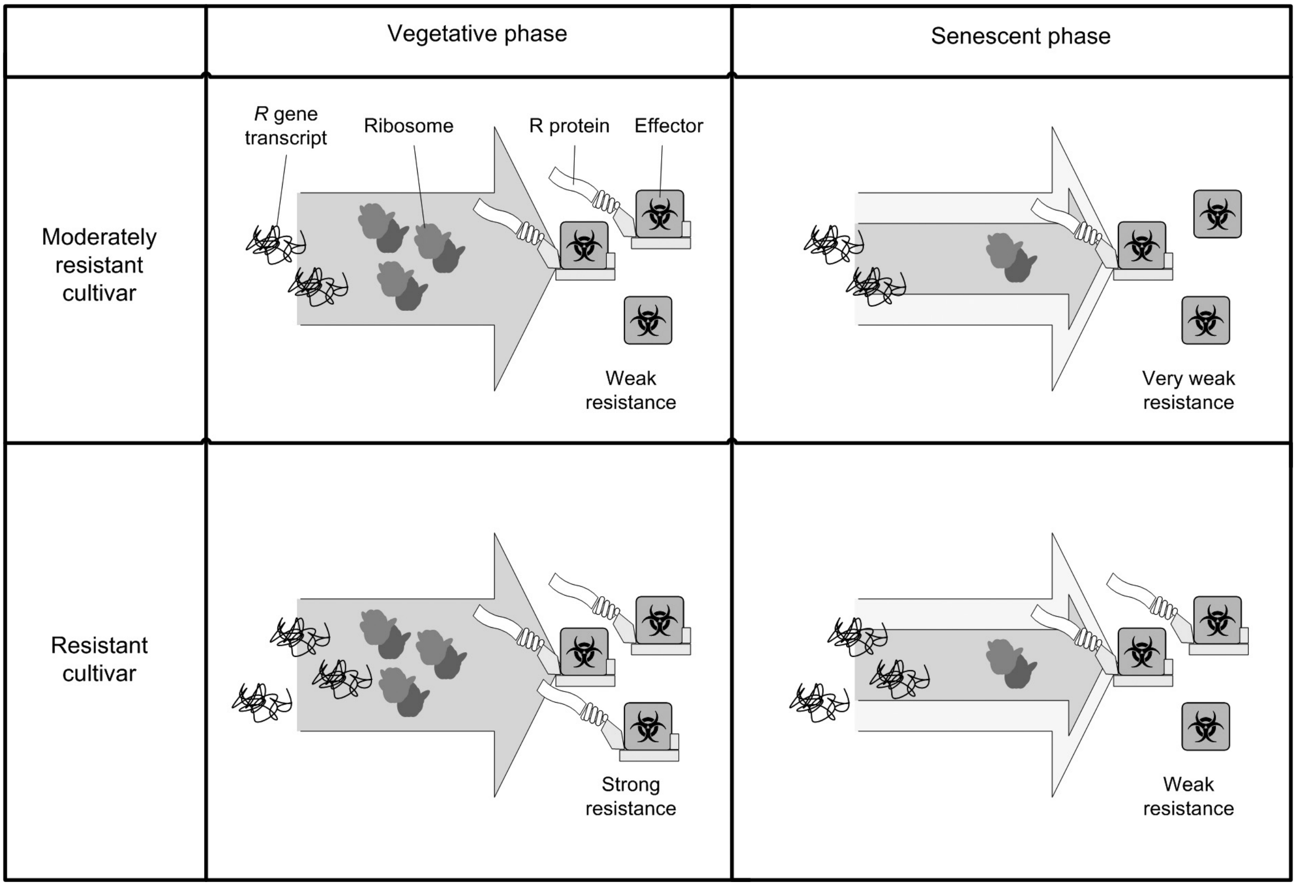

Fig. 2 The 'developmental bottleneck' model. During the vegetative phase (left column) and the senescent phase (right column), transcript levels of resistance genes against *Phytophthora infestans* (*Rpi*) may remain similar; however, they may be lower in moderately resistant cultivars (top row) compared with resistant cultivars (bottom row). As the plant senesces, an assumed decrease in translational capacity could possibly reduce Rpi protein levels. Consequently, susceptibility increases in both genotypes.

30 °C), further indicates little dependence of transcriptional activity on plant age and temperature (Iorizzo *et al*., 2011). In *RB*-transformed potato cultivars, however, transgene copy number and transcript levels were positively correlated with late blight resistance (Bradeen *et al*., 2009; Millett *et al*., 2009), and *RB* transcript levels during the first 24 h post-inoculation (hpi) were a major determinant of *RB*-mediated late blight resistance level (Kramer *et al*., 2009). Plant age and environmental temperature hardly influenced *RB* transcript levels. However, changes in molecules affecting the stability of *Rpi* transcripts or proteins, or changes in translation potential, could modify Rpi protein levels, and thus the degree of resistance. In our own unpublished trials with the *Rpi* gene-harbouring potato cultivar MF-II, late blight inoculation was followed by a decline in transcripts associated with ribosome biosynthesis, translation and glycolysis, which was specific to short-day-conditioned and thus ripening plants. Speculating that the transcription of *SRpigs* is relatively independent of plant age, we propose the hypothesis depicted in Fig. 2. In the post-flowering, near-senescent or senescent stage, translation of *SRpig* transcripts could be reduced, which would negatively affect resistance. However, there are also alternative causes possible. If the decrease in resistance is really caused by a decline in ETI, it could also result from a decrease in components active in signalling or defence. In this context, the question emerges as to whether day-length-conditioned physiological age influences transcript and protein levels of other components of *SRpig*-based resistance, the concentration of cellular energy equivalents and the membrane potential.

Rpi–Avr INTERACTION AND RESPONSE—MOLECULAR FUNCTIONAL MECHANISMS

Recently, molecular interactions of the four *P. infestans* RXLR effectors, Avr2, Avr3a, Avr-blb1 and Avr-blb2, have been partially elucidated, indicating heterogeneity among CNLs with regard to localization and response mechanisms.

Avr2 is localized inside the host nucleus and cytoplasm, but mainly at the perihaustorial plasma membrane, associated with and mediating the interaction of the putative plant phosphatase BSU-LIKE PROTEIN1 (BSL1) with R2 (Saunders *et al*., 2012). Avr-blb2 accumulates at the perihaustorial plasma membrane, where it binds to and inhibits the secretion of the host papain-like cysteine protease (PLCP) C14 (Bozkurt *et al*., 2011). IPI-O1, which has Avr-blb1 activity (Chen *et al*., 2012), binds to an *Arabidopsis thaliana* lectin receptor kinase, thereby disrupting cell wall–plasma membrane adhesion (Senchou *et al*., 2004; Gouget *et al*., 2006). Avr3a inhibits infestin 4-triggered cell death during the biotrophic phase via the stabilization of the host ubiquitin E3 ligase CMPG1 (Bos *et al*., 2010).

Several findings have suggested a role for certain non-Rpi R proteins in defence gene expression. Nuclear location is essential to the function of N (Burch-Smith *et al*., 2007). Furthermore, in the presence of the corresponding effector Avr_{A10}, nuclear *Hordeum vulgare* resistance protein MLA10 associates with the HvWRKY2 transcription factor, which represses genes involved in basal resistance (Shen *et al*., 2007).

The association of Avr2, BSL1 and R2 corresponds to a three-molecule interaction as described by the guard model and the decoy model. Corroborating evidence for the guard and decoy hypothesis has also been obtained for interactions of Solanaceae spp. with other pathogens, i.e. in the guard/bait/Avr systems Prf/Pto/AvrPto (tomato; Mucyn *et al*., 2006), Cf-2/Rcr3/Avr2 (tomato; Rooney *et al*., 2005) and N/NIP1/p50 (tobacco; van Ooijen *et al*., 2007). Interestingly, binding of the guardee Rcr3^{pim} by the *Cladosporium fulvum* Avr2 protein is detected by Cf2 in tomato, whereas its association with *P. infestans* effectors EPIC1 or EPIC2B does not trigger innate immunity (Song *et al*., 2009). Direct Avr–R protein binding supposedly involves the LRR domain, which could subsequently release the R protein from autoinhibition. This is expected to result in a conformational change of the NB-ARC domain and the exchange of ADP for ATP (Takken and Goverse, 2012)

Figure 3 depicts known interactions of ETI components. The components of ETI are listed in Table 3.

Calcium influx and apoplastic alkalinization (Piedras *et al*., 1998), the activation of mitogen-activated protein kinases (MAPKs; Ligterink *et al*., 1997; Romeis *et al*., 1999), the production of reactive oxygen species (ROS; Piedras *et al*., 1998) and transcriptional reprogramming within 30 min (Durrant *et al*., 2000) have been postulated as the earliest events in *R*-gene-based resistance in plants. Suppression of the host HR by RXLR effectors is presumably crucial during the early biotrophic stage of infection by hemibiotrophs (Tyler, 2009).

Several studies have shed light on *Rpi-blb1*-mediated late blight defence mechanisms (Song *et al*., 2003; Vleeshouwers *et al*., 2008). Although the level of transcripts encoding PR-1b, PR-2a, PR-5 and the HR-associated Hin1 increased moderately in susceptible and *RB*-harbouring partially resistant plants for only roughly 48 hpi and then remained elevated, an increase in transcript levels of the same genes was observed for 96 hpi in the resistant cultivar carrying *R9* (Chen and Halterman, 2011). As the timing of HR induction and the onset of *PR* gene expression were similar in partially resistant *RB* plants and immune *R9* plants, the same authors proposed that partial resistance genes, such as *RB*, could trigger molecular mechanisms similar to *SRpigs*, which confer immunity, but may differ in timing and/or intensity of the elicited defence responses.

Potato plants of the cultivar Katahdin transformed with the *RB* gene differed from untransformed Katahdin plants by a consistent, instead of a decreasing, protein level of ribulose bisphosphate carboxylase small chain 2A, by the lack of the oxygen-evolving enhancer protein 1, by an increase, instead of constant, ascorbate peroxidase (APX) levels, and by larger amounts of Qor-like protein after inoculation with *P. infestans* (Liu and Halterman, 2009).

The *R*-gene-based resistance may result from rapid post-infectional biosynthesis of antimicrobial phytoalexins (Ingham, 1973; Müller and Börger, 1940), which, in the Solanaceae family, include polyacetylenes, coumarins, stilbenoids, isoflavans, isoflavones and sesquiterpenoids (Harborne, 1999;

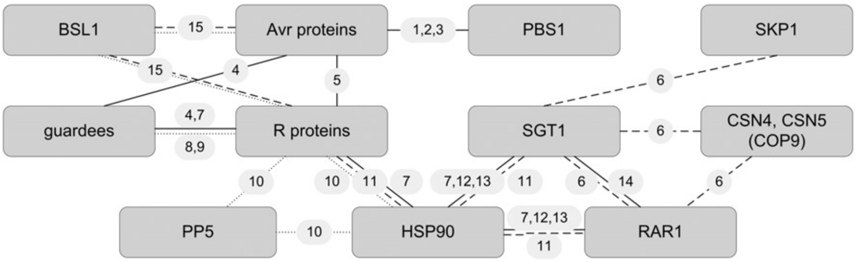

Fig. 3 Molecular interactions of effector-triggered immunity (ETI) components in different pathosystems. Full lines depict interactions in the host *Arabidopsis thaliana*, broken lines in *Nicotiana benthamiana* and dotted lines in *Solanum lycopersicum*. Avr, avirulence; BSL, BSU-LIKE PROTEIN; COP, CONSTITUTIVE PHOTOMORPHOGENIC; CSN, COP9 signalosome; HSP, heat shock protein; PBS, avrPphB susceptible; PP, protein phosphatase; RAR, required for Mla12 resistance; SGT, suppressor of the G2 allele of skp1; SKP, S phase kinase-associated protein. References: 1, Warren *et al*. (1999); 2, Swiderski & Innes (2001); 3, Shao *et al*. (2003); 4, Mackey *et al*. (2003); 5, Deslandes *et al*. (2003); 6, Liu *et al*. (2002b); 7, Hubert *et al*. (2003); 8, Rathjen *et al*. (1999); 9, Mucyn *et al*. (2006); 10, de la Fuente van Bentem *et al*. (2005); 11, Liu *et al*. (2004); 12, Hubert *et al*. (2009); 13, Boter *et al*. (2007); 14, Azevedo *et al*. (2002); 15, Saunders *et al*. (2012).

Table 3 Further components of effector-triggered immunity (ETI) in different pathosystems.

ETI component	Species	Reference(s)
COI1	*Solanum lycopersicum*	Ekengren *et al*. (2003)
L19 (ribosomal protein)	*S. lycopersicum*	Gabriels *et al*. (2006)
MAPKKs (MEK1, MEK2), MAPKs	*S. lycopersicum*	Ekengren *et al*. (2003)
NPR1	*S. lycopersicum*	Ekengren *et al*. (2003)
NTF6	*S. lycopersicum*	Ekengren *et al*. (2003)
RCR3	*S. lycopersicum*	Dixon *et al*. (2000)
TGA1a, TGA2.2	*S. lycopersicum*	Ekengren *et al*. (2003)
WIPK	*S. lycopersicum*	Ekengren *et al*. (2003)
BSL1	*S. lycopersicum, Nicotiana benthamiana*	Saunders *et al*. (2012)
EDS1	*N. benthamiana*	Peart *et al*. (2002)
L30 (ribosomal protein)	*N. benthamiana*	Lu *et al*. (2003)
MAPKK (MEK2)	*N. benthamiana*	Jin *et al*. (2003)
NRG1	*N. benthamiana*	Peart *et al*. (2005)
SIPK	*N. benthamiana*	Jin *et al*. (2002, 2003)
snRNA associated proteins	*N. benthamiana*	Lu *et al*. (2003)
WIPK	*N. benthamiana*	Jin *et al*. (2002, 2003)
RAR2	*Hordeum vulgare*	Jørgensen (1988, 1996), Freialdenhoven *et al*. (1994)
WRKY1, WRKY2	*H. vulgare*	Shen *et al*. (2007)
MPK6	*Arabidopsis thaliana*	Menke *et al*. (2004)
NIM1	*A. thaliana*	Delaney *et al*. (1995)
PBS2, PBS3	*A. thaliana*	Warren *et al*. (1999), Swiderski & Innes (2001)
EDS1	*A. thaliana*	Aarts *et al*. (1998), Falk *et al*. (1999), Parker *et al*. (1996)
NDR1	*A. thaliana*	Aarts *et al*. (1998), Hubert *et al*. (2003)
NPR1	*A. thaliana*	Parker *et al*. (1996)
PAD4	*A. thaliana*	Feys & Parker (2000), Parker *et al*. (2000), Austin *et al*. (2002)
Salicylic acid	*A. thaliana*	Delaney *et al*. (1994), Mauch-Mani & Slusarenko (1996)

Table 4 Online resources for potato and late blight (*Phytophthora infestans*) information.

Description	URL
Solanaceae genomic DB and online tools	http://solanaceae.plantbiology.msu.edu/
Solanaceae genomic, genetic, phenotypic and taxonomic DB	http://solgenomics.net/
Gateway to several DB and tools, e.g. SolEST	http://www.eu-sol.net/
Tomato functional genomics DB	http://ted.bti.cornell.edu/
Potato chromosomal map DB including details such as sequence, gene function and links	http://www.gabipd.org/projects/Pomamo/
Solanum *R* gene DB including phenotypic, genetic, phylogenetic data, germplasm access	http://www.plantbreeding.wur.nl/SolRgenes/
Field data on isolate abundance, cultivar resistance, fungicide efficiency	http://www.euroblight.net
European cultivated potato DB	http://www.europotato.org
Potato pedigree DB	http://www.plantbreeding.wur.nl/potatopedigree/

DB, database.

Pedras and Ahiahonu, 2005), such as capsidiol (Shibata *et al*., 2010).

Although *StCathB* transcript levels peaked at 15 hpi in the incompatible potato–late blight interaction, they slowly increased during 72 hpi in the compatible interaction. Although the induction of components of the 9-lipoxygenase (9-LOX) pathway, which produces several oxylipins toxic to *P. infestans* (Prost *et al*., 2005), has been shown (Kolomiets *et al*., 2000), *R1*-based resistance of *S. tuberosum* to *P. infestans* remained unaffected by RNAi-mediated down-regulation of key enzymes of the 9- and 13-LOX-derived oxylipin pathways, namely 9-LOX, 9-divinyl ether synthase, allene oxide cyclase, 12-oxophytodienoic acid reductase 3 and coronatine-insensitive 1, suggesting that neither 9-LOX-derived oxylipins nor jasmonic acid are essential for *R1*-based resistance of potato (Eschen-Lippold *et al*., 2010).

DETECTION SPECIFICITY

High sequence similarity between *R* genes or R proteins does not necessarily imply close taxonomic specificity. In the *Solanum* spp.–*P. infestans* system, as well as in other plant–pathogen pathosystems (Grube *et al*., 2000), identical or slightly altered taxonomic specificity may result from minor changes in *R*-gene sequence (Champouret, 2010; Li *et al*., 2011; Lokossou *et al*., 2009, 2010; Pel *et al*., 2009; Vleeshouwers *et al*., 2008), as well as from larger ones, as in the case of R3a and R3b, sharing only 65%, and Rpi-blb1 and Rpi-bt1, sharing only 78%, amino acid identity (Oosumi *et al*., 2009). However, Rpi-blb2 and Mi-1 share 82% amino acid identity and confer resistance to such different organisms as *P. infestans* and nematodes, aphids and white fly (van der Vossen *et al*., 2005), and Rx1 and Gpa2 of potato share 88%

identity, conferring resistance to either *Potato virus X* (PVX) or *Globodera pallida* (van der Vossen *et al*., 2000). In remarkable contrast with the idea that broad-spectrum resistance results from an R protein guarding the target of multiple effectors (Nombela *et al*., 2003; Vos *et al*., 1998), the broad-spectrum SRpip RB interacts directly with IPI-O1 and IPI-O4, whereas narrow-spectrum R2-based resistance requires association with a third protein, BSL1.

Some SRpips recognize multiple Avr proteins (van Poppel *et al*., 2009a), and some Avr proteins elicit responses by several different SRpips (Lokossou *et al*., 2009, 2010; Vleeshouwers *et al*., 2008). Both phenomena may possibly result from ancestral effectors or *R* genes after taxonomic diversification events. Mechanistically, the detection of multiple effectors could theoretically arise from: (i) the structural similarity of effectors; (ii) a common bait of these effectors; or (iii) several different baits being associated with the same R protein. The modern discipline of effectoromics examines and instrumentalizes R–Avr interaction specificities to screen for new *R* genes (Vleeshouwers *et al*., 2008); hitherto explored activating (incompatible) R–Avr pairs were listed recently by Champouret (2010), and a more detailed and comprehensive overview can be found elsewhere (Halterman *et al*., 2010; Morgan and Kamoun, 2007; Oh *et al*., 2009, 2010).

MOLECULAR BASIS OF AVIRULENCE AND VIRULENCE OF EFFECTORS

The RXLR domain is not required for elicitor activity of PiAvr4 (van Poppel *et al*., 2008) or Avr3a (Bos *et al*., 2006). The C-terminal half of effectors and its W motifs obviously play a prominent role in (a)virulence activity. A proline at amino acid 129, which is located within the W motif, has been demonstrated to be a determinant of virulence for IPI-O1 and IPI-O4 (Chen *et al*., 2012) and, within a putative recombination between an IPI-O4 and another IPI-O family member (Halterman *et al*., 2010), it is assumed to increase the aggressiveness of the Guatemalan isolate 68 (Chen *et al*., 2012). The dependence of virulence on the W motif has also been shown for both Avr3a and Avr4.

With position 103 placed within the single W motif (Dou *et al*., 2008a), a two-amino-acid change from $K^{80}I^{103}$ to $E^{80}M^{103}$ reduced the avirulence activity of Avr3a (Armstrong *et al*., 2005; Bos *et al*., 2010), the relocalization of Avr3a and R3a to late endosomes (Engelhardt *et al*., 2012) and the suppression of INF1-triggered cell death (Bos *et al*., 2010). PiAvr4 contains the three W motifs W1–W3, of which W2, in combination with either W1 or W3, is required to trigger an *R4*-based HR, therefore determining virulence (van Poppel *et al*., 2009a). The virulence of *P. infestans* isolates towards potatoes harbouring *R4*, however, is also caused by frameshift mutations and truncations, also indicating major changes, but not the 27 single amino acid changes in Avr4, as the divergence of *P. infestans* and *P. mirabilis* served to remove PiAvr4 activity (van Poppel *et al*., 2008, 2009a, b). Likewise, the C-terminal region determines the virulence or avirulence activity of RXLR-dEER effector Avrblb2 from *P. infestans*, and Avr1b from *P. sojae* (Bos *et al*., 2006; Oh *et al*., 2009): Mutations from Val^{69}, Ala^{69} or Ile^{69} to Phe^{69} in Avrblb2 caused a lack of avirulence activity (Oh *et al*., 2009).

Variations in 10 amino acids within the C-terminal region, as well as truncations affecting the WD40 domain, also caused avirulence of the putative transcription factor pi3.4 (Qutob *et al*., 2006).

CONCLUSIONS

The draft genomes of several *Phytophthora* spp. have enabled the identification and examination of numerous effector candidates (Haas *et al*., 2009; Jiang *et al*., 2008; Raffaele *et al*., 2010; Wang *et al*., 2008). Recently, the first crystal structure and solution structure models of *Phytophthora* effectors have been published (Boutemy *et al*., 2011; Sun *et al*., 2013; Yaeno *et al*., 2011), and remote homology modelling has enabled the prognosis of the tertiary structure of homologous effectors. Based on the first models (Takken and Goverse, 2012), the tertiary structure of SRpips from the comprehensive candidate lists for several genomes (Andolfo *et al*., 2013; Jupe *et al*., 2012; Tomato Genome Consortium, 2012) may be estimated. The continued structural classification of effectors and R proteins holds the potential to increase the efficiency of effector screens. These will be required for precise and rapid verification of effector and *SRpig* candidates. The identification of only 68 functional *SRpigs* to date, compared with the large number of candidates and the existence of roughly 1500 *Solanum* spp., indicates the presumably widely unexploited potential of *SRpig*-mediated resistance. For the identification of further interaction partners in ETI, yeast two-hybrid screens with SRpips, effectors, ligands such as BSL1, PI(3)P, chaperones, and combinations thereof, may be helpful. This will possibly also lead to the recognition of further components, such as SGT1 and RAR1. The roles of predicted glycosylation, myristoylation and phosphorylation sites (Ballvora *et al*., 2002; van der Vossen *et al*., 2003) remain to be elucidated. A major challenge will be the analysis of the steric interaction of effectors and SRpips; the analysis of combinations with presumably direct interaction (e.g. Rpi-blb1, Avr-blb1) could precede the analysis of increasingly complex interactions of several molecules (e.g. R2, BSL1, PiAvr2). Supplemented by functional analyses with targeted mutations, structures essential for effector reception and activity will become more apparent. The combination of targeted mutation-based findings with interaction models will also enable better insight into the functions of domains and conserved motifs, such as the K motif, which is frequently found in the 1b3a family (Sun *et al*., 2013).

The availability of completely sequenced genomes (Potato Genome Sequencing Consortium, 2011; Tomato Genome Consortium, 2012) has enabled further approaches. Jupe *et al*. (2012) classified the potato CNL candidates into nine subgroups, several of which do not contain any functionally characterized *SRpigs*. Do *SRpigs* exist which, in contrast with the hitherto functionally analysed *SRpigs*, do not belong to subgroups 1, 4, 5, 6 or 8? Given the hitherto limited structural discernibility of *SRpigs* and other CNLs, a comparison of *SRpigs* with non-*SRpig R* genes may possibly reveal further structural characteristics typical for *SRpigs*. Do SRpips exist, which belong to other classes, such as the TNL, RLK or RLP class? Further examination of determined resistance loci and cloning of *SRpigs*, such as *Rpi-cap1*, *Rpi-qum1*, *Rpi-avl1* and *R4*, which share a locus with the TNL class gene *N* on chromosome XI, will possibly answer this question.

Furthermore, the sequenced genomes will provide further insight into the evolution of *R* genes, and therefore allow conclusions to be drawn on which evolutionary processes have proved to be advantageous.

SRpigs are not distributed evenly, but cluster together at genomic positions well conserved between *Solanum* spp., enabling approaches, such as synteny-based gene localization and isolation, to be employed. Genomic locations of *SRpigs* and RGAs are not independent from, but associated with, late maturity, as is the case for quantitative resistance. However, the fact that very early cultivars harbouring *R1* or *R3* exist suggests the existence of *Rpi* loci without linkage to maturity. Do other genes involved in ETI signalling or defence possibly co-localize to *R*-gene clusters?

According to the guard model and the decoy model, the recognition specificity would not necessarily depend solely on R proteins. Instead, secondary molecules functioning as baits could adapt the switch feature of R proteins to diverse effector topologies. Theoretically, recognition capacity might therefore be multiplied, limited by the number and affinity of the bait molecules. Conversely, several *R* genes could associate with the same bait, which possibly could be the case for BSL1 and PiAvr2. PiAvr2 is recognized by R2, R2-like, Rpi-abpt, Rpi-blb3, Rpi-edn1.1, Rpi-snk1.1, Rpi-snk1.2 and Rpi-hjt1.1–Rpi-hjt1.3. These receptors partially share only 92.1% amino acid identity (Champouret, 2010). For Rpi-blb1 and IPI-O, however, direct interaction has been observed *in vitro* (Chen *et al*., 2012). In contrast with the receptors detecting PiAvr2, these receptors (Rpi-blb1, Rpi-sto1, Rpi-pta1) share at least 99.6% amino acid identity. Similarly, receptors detecting Avr3a (R3a, Rpi-sto2) and Avr-vnt1 (Rpi-vnt1.1–Rpi-vnt1.3) share at least 99.7% and 98.2% amino acid identity, respectively. This could possibly be an indication for a more direct interaction between *SRpigs* and effectors in comparison with the case of PiAvr2. However, initial experiments did not reveal a direct interaction of R3a and Avr3a (Engelhardt *et al*., 2012)

Interaction sites of numerous effectors which suppress both PTI and ETI (Wang *et al*., 2011) remain to be determined. Depending on the oomycete–host pathosystem, PRRs are selectively absent from the extrahaustorial matrix (Koh *et al*., 2005; Lu *et al*., 2012; Micali *et al*., 2011), evoking the question of whether some effectors (Oh *et al*., 2009; Wang *et al*., 2011) might possibly interfere with PRR synthesis and/or localization.

Finally, there is the need to examine the relevance and effects of the various putative influences on transcript and protein levels (Cooke *et al*., 2012). Very recently, evidence has been found that host- and pathogen-owned RNAi mechanisms could affect both *R* genes (Tomato Genome Consortium, 2012) and effectors (Vetukuri *et al*., 2012), and that some effectors may suppress the host-encoded RNA silencing machinery (Qiao *et al*., 2013). Our knowledge on SRpigs and RXLR effectors has increased tremendously during the last decade. However, many issues of R-protein–effector interaction, signalling and defence remain to be elucidated. The role of CRN and other non-RXLR effectors remains largely unexplored, and *Rpi* gene-based resistance remains an important and exciting field of research.

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