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REVIEW

Late Blight resistance in potato: An Indian perspective

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When it comes to potato illnesses, late blight is thought to be the most significant fungal disease. It is brought on by *Phytophthora infestans*, a reemerging pathogen that regularly emerges new strains with heightened virulence and shows up in unexpectedly intense new sites. The exceptional capacity of this destructive pathogen to quickly adapt to control techniques, like the use of fungicides and resistant cultivars, presents a challenge to management. To tackle this terrible disease, an integrated combination of methods is necessary, as no single technique has proven beneficial for its care. The disease, the pathogen and its population structure, the nature of disease resistance, the structure and function of resistance genes, and recent developments in breeding for resistance have all been attempted to be covered in this communication.

Keywords : Late blight, *Phytophthora infestans*, R gene

INTRODUCTION

Potato (*Solanum tuberosum* L.) is the third most important food crop after rice and wheat in terms of human consumption and is regarded as one of the most important crops for addressing food security challenges, especially in developing countries. More than a billion people consume potato on a regular basis globally, and it is an important source of income for millions of farmers (Devaux *et al.* 2014). Presently, the crop is raised in 17.79 million hectares with 375 million tonnes of global production with an average yield of ~21 t/ha (FAOSTAT 2024). Potato production increased noticeably in many countries throughout the world during last two decades because of area expansion and improvements in yield. Global statistics indicate that potato production is shifting towards developing countries, especially to Asia and Africa, and potato production in the developing countries has surpassed the developed world since 2006 (FAO, 2008). Worldwide in 2022, China was the largest producer of potatoes with India at second spot (FAOSTAT, 2024).

Though potato is a household name today in India, it came to this ancient agrarian land only about 400 years ago during Mughal dynasty. In the subsequent two centuries and a half after its introduction, Agri-Horticultural societies and the Botanical Gardens took keen interest in promoting its cultivation throughout India. The Royal Agri-Horticultural Society founded by the great missionary scholar William Carrey in the year 1820 at Kolkata was one of such societies that popularized potato cultivation in eastern India. Though potato production has increased considerably since 1960s in the developing world including India, the sustainability of potato production is still threatened by multitude of adverse biotic and abiotic stresses. The crop is susceptible to numerous oomycete, fungal, and bacterial diseases, phytoplasmas, more than three dozen viruses of the yellow and mosaic groups and several parasitic nematodes.

Diseases of potatoes include arguably the most historically significant crop disease, late blight,

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which is still the most important potato disease. *Phytophthora infestans* (Mont.) de Bary (1876), the causal organism of potato late blight, is considered as a re-emerging pathogen due to regular emergence of novel strains with increased virulence and its appearance in new locations with surprising intensity (Fry *et al*. 2015; Sharma *et al*. 2016; Dey *et al.* 2024). Management of this devastating pathogen is challenged by its remarkable ability to quickly adapt to control strategies such as deployment of resistant cultivars and fungicides. Since no single approach is effective for its management, combination of approaches in an integrated manner is essential to combat this devastating disease. Nevertheless, late blight resistant cultivars constitute the corner stone of the integrated management of potato late blight. In the present communication, efforts have been made to discuss about the disease, the pathogen & its population structure, nature of disease resistance, structure and function of resistance genes, and recent advances in breeding for resistance.

THE DISEASE

Potato late blight is the most important disease of potato worldwide. Historically, it was primarily responsible for the infamous Irish potato famine during 1845-47 that drastically changed the course of European history. After its first introduction in Spain's Canary Islands in the year 1565 from South America, potato gradually spread to Italy, Belgium, Germany, France, Switzerland and The Netherlands within a span of 40 years and reached England by 1597. It gradually emerged as the most important component of Europe's food security during 1750 to 1850, since it has the ability to produce twice the calories of rye and wheat per unit area. *P. infestans* originated in the Toluca valley of central Mexico and migrated to the United States in early 1843. Unregulated trade in potatoes between USA and Europe during 1840s probably facilitated its quicker migration to Ireland and arrival of a particularly aggressive strain (HERB-1) from USA altogether changed the potato scenario in Europe by 1845. The strain was exceptionally virulent and spread like wild fire in large acreage of susceptible potato crop causing a devastating famine in Ireland (Martin *et al.* 2013, 2014; Yoshida *et al.* 2013, 2014). The worst year of the famine was 1847, which became known as "Black '47". During that Great Famine, roughly 1 million people died and more than 1 million more fled the country, causing the country's population to fall by 20–25% (in some towns, populations fell as much as 67%) between 1841 and 1871. Between 1845 and 1855, at least 2.1 million people left Ireland, primarily on packet ships but also on steamboats and baroques - one of the greatest exoduses from a single island in history. In addition to the well-documented Irish potato famine, crop failures in 1845 and 1846 contributed to an estimated 750,000 hunger-associated deaths in continental Europe (Zadoks, 2008).

Till today, late blight remains a major constraint to potato production globally and is thus a constant threat to food security (Cooke *et al*. 2012, Fisher *et al.* 2012, Haverkort *et al.* 2008). Losses due to potato late blight have been estimated as € 12 billion per annum of which the losses in developing countries have been estimated around € 10 billion per annum (Haverkort *et al*. 2009). Studies conducted in the United States to estimate the impact of late blight on potato yield and fungicide use revealed that use of the fungicides alone costs $ 77.10 million at an average cost of around $ 507 per ha which do not include non-fungicide control practices (Guenthner *et al*. 2001). Region-wise economic importance of late blight shows that the disease inflicts highest loss in Sub-Saharan Africa (44% crop losses) followed by Latin America (36%), Caribbean (36%), South-East Asia (35%), South-West Asia (19%) and Middle East and North Africa (9%).

Late blight came to India with imported seed potatoes from Europe. It was first recorded between 1870 and 1880 in the Nilgiri hills and spread rapidly to North-Indian hills. From hills the disease gradually spread to Indo-Gangetic plains. Presently, it appears every year in the hills and once in 2-3 years in devastating form, in the plains. Losses caused by this disease in the hills may go as high as 85%, if the varieties grown are susceptible and are not protected by fungicide sprays. This disease is also known to cause losses up to 60-70% in the plains in some years.

On overall basis, it inflicts annual losses up to 15% which comes to a loss of 7.95 million tonnes of potatoes.

Late blight affects both above and below ground parts of potato. The pathogen adopts a two-step infection style typical of hemi-biotrophs. Infection generally starts when sporangium lands on a plant surface and release zoospores that encyst, germinate, and penetrate the host tissue or sporangia directly germinate and initiate the infection. Germ tubes form an appressorium and then a penetration peg, which pierces the cuticle and penetrates an epidermal cell to form an infection vesicle. Branching hyphae with narrow, digit-like haustoria expand from the site of penetration to neighboring cells through the intercellular space. At this biotrophic phase *P. infestans* requires living cells to obtain nutrients. This stage of infection remains unnoticed to the naked eye, but at cellular level a repertoire of molecular interactions takes place. The first visible symptoms appear within 2–3 days when the pathogen switches to the necrotrophic stage. Later on, the mycelium develops sporangiophores that emerge through the stomata to produce numerous asexual spores that initiate new infections (Judelson and Blanco, 2005). In leaves, water-soaked irregular pale green lesions mostly near tip and margins that enlarge into brown to purplish black necrotic spots appear. A white mildew, which consists of sporangiophores and spores of the pathogen, can be seen on lower surface of the infected leaves especially around the edges of the necrotic lesions under high humidity (Nowicki *et al*. 2012). On stems and petioles light to dark brown lesions encircle the stems as a result the affected stems and petioles become weak at such points and may collapse. Affected tubers show irregular reddish brown to purplish areas which extend into internal tissues of the tubers.

THE PATHOGEN

Potato late blight is caused by the oomycete pathogen, *Phytophthora infestans* (Mont.) de Bary (1876). The pathogen was first described by C. Montagne in France and Reverend M. J. Berkeley as *Botrytis infestans* (Montagne, 1845, Berkeley, 1846). Morren had observed the disease in Belgium in 1844, called it *Botrytis devastatrix* (Morren, 1844). Libert had also called the pathogen *Botrytis devastatrix* Lib. 1845 (alternate spelling *vastatrix* or *devastrix*), but Berkeley chose to use the species name *Botrytis infestans*. Unger and Caspary considered it in the genus *Peronospora* (Caspary, 1853; Unger, 1847). Heinrich Anton de Bary accepted this opinion in 1863 and then, in 1876, renamed the species *Phytophthora infestans* based on sporangial development and sporangiophore characteristics (de Bary, 1876). The genus name *Phytophthora* comes from the Greek (*phyto*), meaning “plant” – plus the Greek (*phthora*), meaning “decay, ruin, perish”. The species name *infestans* is the present participle of the Latin verb *infestare*, meaning “attacking, destroying”, from which the word “to infest” is derived. In fact, the discovery that late blight was caused by a microbial pathogen, 15 years before Pasteur’s formal confirmation of Germ Theory, was a significant milestone in the foundation of plant pathology as a scientific discipline. *P. infestans* is now considered as the top most oomycete pathogen (Kamoun *et al*. 2015).

P. infestans belongs to the class oomycetes under the domain eukarya. Oomycetes are the members of the Kingdom Chromista (Beakes *et al.* 2012; Cavalier-Smith and Chao, 2006) under Super Kingdom Chromalaveolate (Baldauf *et al*., 2000; Yoon *et al*., 2002). Though members of this class superficially resemble filamentous fungi, they are phylogenetically related to diatoms and brown algae of the clade stramenopiles. The Stramenopiles, also called Heterokonts, are a clade of organisms distinguished by the presence of stiff tripartite external hairs. In most species, the hairs are attached to flagella, in some they are attached to other areas of the cellular surface, and in some they have been secondarily lost. Fossil evidence indicates that a number of oomycetes emerged as endophytes of land plants at least by the Carboniferous period, approximately 300–350 million years ago.

P. infestans is a heterothallic oomycete with both sexual and asexual reproductive cycles. With few exceptions, for example, Toluca Valley, Mexico; Scandinavia; and the Netherlands (Bruberg *et al*.

2011; Fry *et al*. 2015; Yuen and Andersson, 2013), the asexual reproductive cycle dominates resulting in the development of distinct clonal lineages. The vegetative stage of the mycelium in *P. infestans* is diploid, while in true fungi it is haploid. However, recent studies have shown that progenies from sexual *P. infestans* populations in the modern-day lineages are diploid, but the most important pandemic clonal lineages are triploid (Li *et al*. 2017). Waves of migration and genotype displacements in the 20th century have been well documented . The size of the *P. infestans* genome is considerably larger (240 Mb) and by far the largest and most complex genome sequenced so far in the chromalveolates and even in true fungi. The genome has an extremely high repeat content (~74%) and an unusual gene distribution, which is thought to contribute to *P. infestans* evolutionary potential by promoting genome plasticity, thus enhancing genetic variation of effector genes leading to host adaptation (Haas *et al*. 2009). A total of 17,797 protein-coding genes have been detected within the *P. infestans* genome.

Virulence of oomycetes including *P. infestans* depends on rapidly evolving protein families including extracellular toxins, hydrolytic enzymes, and cell entering effectors that help the pathogen suppress the host plant defenses and gain nutrition from the host (Jiang and Tyler, 2012). *P. infestans* secretes large numbers of effectors: apoplastic effectors that accumulate in the plant intercellular space (apoplast) and cytoplasmic effectors that are translocated directly into the plant cell by a specialized infection structure called the haustorium (Whisson *et al.* 2007). Apoplastic effectors include secreted hydrolytic enzymes such as serine protease inhibitor (EPI1 to EPI14); cystatin-like protease inhibitor (EPIC1-EPIC4); glucanase inhibitor (GIP1 to GIP4); small cysteine rich protein (Elicitin INF1, SCR74 & SCR91); NEP1 like protein (NLP) family; CBEL (Cellulose binding, elicitor and lectin: 52 different sequences identified). Cytoplasmic effectors include RxLR families having ~150 aa long N terminal type II secretion signal followed by a conserved RxLR (arginine-X-leucine-arginine) motif; Crinkler (CRN) families of effectors (CRN1, CRN2 and a large family of similar proteins); and IPI-O (*In planta* induced protein). All known *P. infestans* effectors, which are recognized by the products of corresponding potato *Rpi* genes, belong to the RxLR class. The RxLR effectors contain the highly conserved N-terminal motif involved in the translocation of *P. infestans* effector proteins into plant cells, and the heterogeneous C-terminal region that can be recognized by plant *R* gene products (Dou *et al.* 2008). In the genome of *P. infestans*, 563 effector genes with the RxLR motif have been identified (Haas *et al.* 2009) and for 15 of them, the respective potato *Rpi* genes have been identified. Hemibiotrophs, such as *P. infestans*, secretes distinct classes of effector proteins that first suppress plant defense responses and associated programmed cell death (PCD), and later induce large scale necrosis. An effector protein of *P. infestans*, SNE1 (suppressor of necrosis 1) has been described in 2010 (Kelly *et al*. 2010), which is specifically expressed during early biotrophic growth in the host plant tomato. The SNE1 effector suppresses the action of necrosis-inducing effectors like PiNPP1.1 and PsojNIP. Conversely, the PiNPP1.1 of *P. infestans* and PsojNIP of *P. sojae* are induced during necrotrophy. It also suppressed programme cell death (PCD) mediated by Avr-R protein interactions. It suggested that SNE1 and PiNPP1.1 act antagonistically, thereby providing a highly regulated means to control the transition from biotrophy to necrotrophy. The class of effectors known as IpiO (*In planta* induced) are expressed in invading hyphae and is associated with biotrophic growth. IpiO corresponds to the RxLR effector Avr-blb1, which is recognized by the *R* gene encoded protein Rpi-blb1.

LATE BLIGHT RESISTANCE

As mentioned earlier, extreme genome flexibility of *P. infestans* enabling it to adapt quickly to external environment, makes the pathogen a formidable problem to manage. Therefore, continuous refinement of technologies for managing this pathogen in an integrated manner is necessary. Management schedules based on fungicide spray coupled with effective disease forecasting, field sanitation and other cultural & bio-intensive strategies have been developed for management of the disease. Nevertheless, host

resistance still constitutes the most environmentally and economically preferred option globally for the management of late blight. With the use of host resistance, fungicide load can be reduced either by lowering the fungicide dose or increasing the application intervals (Kirk *et al*. 2005; Cooke *et al*. 2011; Haverkort *et al*. 2016). A brief description of different aspects of late blight resistance in potato are given below.

NATURE OF RESISTANCE

Breeding for improving natural resistance of crop plants started during early 20th century. Shortly after scientists became aware of Mendel's law of inheritance, yellow rust resistance in wheat was demonstrated to be inherited in a Mendelian fashion (Biffen, 1905). This stimulated research to identify and incorporate disease resistance in crops through breeding. Breeding for late blight resistance began nearly 100 years ago throughout the world with the introgression of resistance genes from *Solanum demissum*, a wild hexaploid species indigenous to Mexico. Resistance in *S. demissum* is determined by dominant *R* genes inducing hypersensitive (HR) response upon infection with specific races of *P. infestans* (vertical resistance) in a pattern similar to gene-for-gene hypothesis proposed by Prof. Harold H Flor (Flor, 1942). Initially, 11 resistance genes were identified, all originating from *S. demissum* and named *R1* to *R11*. A plant with the gene *R1* is susceptible to race1 (r1) or any other race of *P. infestans* with 1 in its designation, but resistant to r2, r3, and r4 or races with 2,3, or 4 in any combination in their designation. A plant with the two genes *R1* and *R2* is susceptible to r1,2 or any other race with both the number 1 and 2 in it, but is resistant to all other races. The more the resistance genes the clearer it becomes that susceptibility is specific and resistance nonspecific. In a 11 gene system (with 2^{11}=2048 races) a plant with the 11 genes, *R1* to *R11*, is susceptible only to race (1,2,3,4,5,6,7,8,9,10,11). It is resistant to any of the other 2047 races. This was the basis for a differential set of potato lines used worldwide to determine the virulence phenotypes occurring in the pathogen population (Black *et al.* 1953; Malcolmson & Black, 1966; Malcolmson, 1969). Even though resistance was the rule, the race-specific vertical resistance in *S. demissum* was very short-lived due to rapid coevolution of matching avirulence in *P. infestans* in an evolutionary "arm race" (Wastie, 1991). Because of the failure of vertical resistance to provide sustainable protection in the farmers' fields, there was a shift in emphasis on race non-specific horizontal resistance during 1990s (Bradshaw *et al.* 2006). Vertical resistance refers to when a plant variety/cultivar is bred to have complete resistance to particular races or strains of a pathogen which is controlled by a single gene in the host. By contrast, horizontal resistance refers to when a plant variety/cultivar is bred to have a general level of resistance, or incomplete resistance, to many races or strains of a pathogen, which is controlled by multiple host genes (Vanderplank 1963, 1968). This type of horizontal resistance was first analyzed by genetic linkage mapping in a cross of non-inbred *S. tuberosum* dihaploid parents (Leonards-Schippers *et al.* 1994). Since then, QTL mapping for late blight resistance has been done in several diploid wild species such as *S. berthaultii* (Ewing *et al.* 2000), *S. phureja* (Ghislain *et al.* 2001), *S. paucissectum* (Villamon *et al.* 2005), *S. chacoense* (Chakrabarti *et al.* 2014) to name a few. As a result, the factors controlling quantitative resistance have been located on almost every chromosome in potato reflecting the truly polygenic nature of this trait (Tiwari *et al.* 2013). Resistant genes from the wild species *S. demissum*, *S. stoloniferum* and the cultivated *S. tuberosum* subsp *andigena* and *S. phureja* have been utilized to develop commercial potato cultivars in different parts of the world (Bradshaw *et al.* 2006). Introgression of these genes into cultivars sometimes requires interspecific bridge crosses (Hermsen and Ramanna 1973). This approach resulted in the introgression of *Rpi-blb2* from *S. bulbocastanum* into the cultivars Toluca (NL 2006) and Bionica (NL 2008) (Haverkort *et al.* 2009). Nevertheless, it is necessary to continue the search for new sources of resistance in wild gene pools for developing potato cultivars with durable resistance by a blend of conventional and molecular approaches. Genetic engineering may also provide options for generating resistant cultivars. A resistance gene effective against most known strains of late blight has been identified from a wild relative of the potato, *Solanum bulbocastanum*, and introduced by genetic

engineering into cultivated varieties (Song *et al.* 2003; Van der Vossen *et al.* 2003). Introgression of *RB* (Resistance gene from *bulbocastanum*) gene in Indian popular potato cultivars has demonstrated variable level of late blight resistance.

LATE BLIGHT RESISTANCE GENES

Chromosomal positions of many *R* genes from *S. demissum* have already been determined. Eight *R* genes have been mapped; *R1* on chromosome V (Leonards-Schippers *et al.* 1992), *R2* on chromosome IV (Li *et al.* 1998), *R3a* and *R3b* (Huang *et al.* 2004), *R6* and *R7* (El-Kharbotly *et al.* 1996), *R10* and *R11* (Bradshaw *et al.* 2006) on chromosome XI. *R5*, *R8* and *R9* have been suggested to be allelic variants of *R3*, located on chromosome XI (Huang 2005). In fact, more than 70 *Rpi* (*R*) genes have been identified and mapped so far in 32 *Solanum* species. Most of the *Rpi* genes have been derived from tuber-bearing species including 9 species from Mexico, 6 from Bolivia, 4 from Peru, 3 from Argentina, 1 from Paraguay, 1 from USA, and 1 species found generally in the Andes. Novel *Rpi* genes were found also in *S. tuberosum* subspecies *andigena* and in Hungarian cultivar Sárpo Mira. Six *Rpi* genes were identified in four non-tuber-bearing species and five from the tomato wild species *S. pimpinellifolium*. Single resistance genes were identified in 15 potato wild species. Frequently, multiple functional *Rpi* genes have been found within a single species, e.g., *S. demissum* (14 *Rpi* genes), *S. bulbocastanum* (5), *S. berthaultii* (5), *S. stoloniferum* (4), *S. edinense* (4), *S. venturii* (4), *S. hjertingii* (3), *S. chacoense* (3), *S. huancabambense* (2), *S. pinnatisectum* (2), *S. schenckii* (2) and *S. tarijense* (2). The *Rpi* genes were mapped in clusters onto potato chromosomes I, IV, V, VI, VII, VIII, IX, X, and XI. For example, on chromosome IV, a total of 13 *Rpi* genes from seven potato wild species were found. Six QTLs determining late blight resistance have also been mapped - two for sensitivity and four for resistance. Molecular analysis of QTLs revealed that resistance is conditioned by presence of *Rpi* gees (*R8, R10, Rpi-blb1*).

The Potato Genome Sequencing Consortium (PGSC) established in 2005 deciphered and published 727 Mb out of 844 Mb potato genome from the doubled monoploid (DM) *S. phureja* (Xun *et al.* 2011). The sequence revealed that 438 out of 40,000 identified genes in reference genome contain the characteristic NB-LRR domain (Jupe *et al.* 2012), while the dihaploid potato clone RH89-039-15 (*S. tuberosum* ssp. *tuberosum*) contains 738 partial or full-length NLR sequences (Bakker *et al.* 2011). The use of resistance gene enrichment sequencing (RenSeq) led to an increase in the number of identified NLR in the DM reference genome from 438 to 755 (Jupe *et al.* 2013). All twelve potato chromosomes contain genes belonging to the CNL (CC-NB-LRR) and TNL (TIR-NB-LRR) groups, except for chromosomes III and X, on which genes from the TNL group are not found. The majority of NLR genes (57 and 54 in numbers) were found on chromosomes IV and XI, respectively. The fewest number of NLR genes (3 in number) was found on chromosome III. Moreover, the greatest number of NLR gene clusters is on chromosome IV. There are 4.7 times more CNL genes than TNL genes in the analyzed potato genome (Jupe *et al.* 2012). Recently, using Illumina HiSeq 2000 technology, 585 NBS domains, including 11 not previously described, were analyzed in 96 potato genomes (Prakash *et al.* 2020).

Despite rapid breakdown of *R1, R2, R3, R4* and *R10* in the past, *S. demissum* is still considered a valuable source for both race-specific and race-non-specific resistance (Colon *et al.* 1995). Potato differentials MaR8 and MaR9 were shown to be durably resistant to several *P. infestans* isolates (Haynes *et al.* 2002), however, R8 and R9 have never been used in breeding (Huang, 2005). Evaluation of the reaction of potato differentials to over 5,000 *P. infestans* isolates, collected in various parts of the world, showed that the resistances of differentials MaR5, MaR8 and MaR9 were most durable (Swiezynski *et al.* 2000). Also, *P. infestans* isolates derived from clonal lineage US8, the most common and aggressive genotype of *P. infestans* present in the US (Fry and Goodwin, 1997) overcame all known *R* gene differentials except MaR8 and MaR9, both in detached leaf assay and in field trials (Bisognin *et al.* 2002). The MaR8 resistance gene has been mapped on the distal end of the long arm of chromosome IX. Another new *Rpi*

gene from *S. americanum Rpi-amr1*, was positionally cloned and mapped onto the short arm of chromosome XI (Witek *et al.* 2021). A homologue of *Rpi-amr1* has been identified in the non-host species *S. nigrum*. *Rpi-amr1* confers broad-spectrum late blight resistance in cultivated potato. Stably transformed transgenic potato cultivar Maris Piper plants carrying *Rpi-amr1*, resist 19 *P. infestans* isolates tested, including those overcoming *Rpi-vnt1*, *Rpi-blb1* and *Rpi-blb2*. In potato wild species *S. chacoense*, two resistance genes, *Rpi-chc1.1* and *Rpi-chc1.2* have been identified (Monino-Lopez *et al.* 2021). An allele-mining strategy allowed the identification of *Rpi-chc1.1* orthologue in *S. chacoense*, *S. berthaultii* and *S. tarijense* accessions resistant to late blight.

STRUCTURE OF R (*Rpi*) PROTEINS

Though genes specifying resistance have been identified during 1940's, isolation of *R* genes could be attempted only after standardization of molecular techniques for cloning plant genes of unknown structure or molecular function. Techniques like transposon tagging, T-DNA mutagenesis and positional cloning enabled isolation of several *R* genes during the last three decades. The first cloning of a *R* gene was achieved through transposon tagging of *Hm1* from maize that encodes an NADPH-dependent carbonyl reductase detoxifying HC-toxin produced by race 1 strains of *Cochliobolus carbonum*. Unfortunately, studies of *Hm1* did not suggest a structure or function for classically defined *R* genes because the toxin degrading strategy of *Hm1* does not involve pathogen *Avr* genes, induction of hypersensitive plant cell death, or other hallmarks of gene-for-gene interactions. First classical *R* gene (*Pto*, a serine-threonine kinase) was isolated from tomato by positional cloning (Martin *et al.* 1993). This gene was found to encode a protein with similarity to serine-threonine kinases. Perfection of molecular techniques like chromosome walking, resistance gene enrichment sequencing (RenSeq), diagnostic RenSeq (dRenSeq), generic-mapping enrichment sequencing (GenSeq), single-molecule real-time sequencing (SMRT RenSeq) etc. enabled cloning of a large number of *Avr*-gene specific *R* genes from diverse host-pathogen systems. The resistance genes that were isolated bore a striking similarity to each other but had no apparent resemblance to *Pto*. Most of the plant resistance (*R*) genes are members of a large gene family that encodes nucleotide-binding site and leucine-rich repeat (NB-LRR; NLR) domain-containing proteins (Lozano *et al.* 2015). On the basis of the structure of NLR proteins, two main groups can be distinguished. The first is the so-called TIR-NB-LRRs (TNLs) with N-terminal domain homologous to the Drosophila Toll domain and human interleukin-1 receptor. The second group is non-TIR-NB-LRRs known as CNLs, which contains coiled coil (CC) structure or leucine zipper (LZ) motif in N-terminal region (Ballvora *et al.* 2002; Sekhwal *et al.* 2015). Most of the *Rpi* genes are intron-free and the size and structure of different *Rpi* genes, as well as of different alleles of the same *Rpi* gene, are diverse. Examples of the longest *Rpi* genes include *Rpi-amr1-2307* (7,277 bp) from *S. americanum* and *Rpi-blb2* from *S. bulbocastanum* (4,858 bp) belonging to the CC-NB-LRR class, and *R1* from *S. demissum* (4,102 bp) which is part of LZ-NBLRR group (Paluchowska *et al.* 2022). The shortest genes include *R2* family members, e.g., *R2* from *S. demissum* (2,538 bp), *Rpi-edn1.1* from *S. edinense* (2,544 bp), *Rpi-hjt1.1*, *Rpi-hjt1.2* and *Rpi-hjt1.3* from *S. hjertingii* (2,544 bp). These genes are located on chromosome IV and are members of the LZ-NB-LRR group. The size of the identified alleles of *Rpiamr1* ranged from 2,768 to 7,277 bp and the number of introns range from one to four. Molecular cloning of the *Rpi* genes facilitated studies on potato late blight resistance at the molecular level (Ballvora *et al.* 2002). The cloned genes can be used in genetic engineering to develop late blight resistant cultivars.

BREEDING FOR DURABLE RESISTANCE

Global effort by Prof. William Black and his group at Scottish Crop Research Institute (now James Hutton Institute) to introgress *R* genes from *S. demissum* was initiated by mid 1950s. *R* gene introgression from wild relatives of the potato into commercial cultivars through crossing was time-consuming, especially in the case of species separated from cultivated potato by crossing barriers such as different endosperm balance

numbers (EBNs). For example, the introgression of a single *R* (*Rpi*) gene (*Rpi-blb2*) from the wild species *Solanum bulbocastanum* to potato cultivars Bionica and Toluca necessitated more than 45 years (Haverkort *et al.* 2016). Unfortunately, most of the resistant varieties developed by classical breeding were defeated very quickly because the resistance genes targets, the RxLR effector genes of *P. infestans*, evolve very rapidly through gene insertions and deletions, complete gene deletions, point mutations (SNPs), present and absent variation (PAV), and gene silencing, avoiding interactions with the *R* genes. On average, resistance conferred by *R* gene in potato varieties persisted for 5 - 10 years, and then the variety becomes susceptible to new races of *P. infestans*. In fact, breeding for race-specific vertical resistance was discontinued by 1990s and search for durable resistance was intensified. According to the gene-for-gene concept, specific *R* protein of potato is activated by cognate pathogen effector. However, some *R* proteins can recognize multiple effectors of *P. infestans* and *vice versa*, thereby conferring broad-spectrum resistance. More than 20 genes conferring broad spectrum resistance have been discovered, with all of them having an N-terminal motif containing two loops (NB-LRR). Broad spectrum resistance can be conferred by single (*Rpi2*, *R3a*, *Rpi-blb2*, *Rpi-rzc1*, *Rpi-ver1*, *Rpi-amr1*) or pyramided *Rpi* genes (*Rpi-blb2* + *Rpi-vnv1.1* in C88 cultivars). The *Avr2* effector can be recognized by not only *R2* protein from *S. demissum* but also by *Rpi-blb3* from *S. bulbocastanum*, *Rpi-mcq1* from *S. mochiquense*, *Rpi-hcb1.1* and *Rpi-hcb1.2* from *S. huancabambense* (Aguilera-Galvez *et al.* 2018, 2020). The *Rpi* genes encoding these proteins are located on different chromosomes, *R2* and *Rpi-blb3* on chromosome IV, *Rpi-mcq1*, *Rpi-hcb1.1* and *Rpi-hcb1.2* on chromosome IX. In some cases, different alleles from the same *Rpi* gene can recognize different effectors which belong to the same RxLR family (Monino-Lopez *et al.* 2021). Protein products of *Rpi-chc1.1* and *Rpi-chc1.2* which are allelic variants recognize two different effectors within the same effector class *Avrchc1.1* and *Avrchc1.2*, respectively. The LRR domain is involved in the recognition of cognate effector and changes in its structure may lead to the loss of the ability to recognize the effector or to shift the recognition ability from one effector to another. Exchange of the LRR domain in the chimeric receptors changed the recognition spectrum of the *Avrchc1.1* to *Avrchc1.2* (Monino-Lopez *et al.* 2021). In principle, the effectors of *P. infestans* that are essential for infection cannot be mutated by the pathogen without a fitness cost and loss of pathogenicity. R proteins recognizing such essential effectors would likely provide broad-spectrum and durable resistance. *P. infestans Avr3a*, especially virulent allele *Avr3a EM*, may be an example of an essential effector since this gene is conserved among diverse *P. infestans* strains and is highly expressed at the early stage of infection (Yin *et al.* 2017). Similarly, *Avrpi-blb1* and *Avrpi-blb2* are quite conservative in *P. infestans* thus enabling durability of *Rpi-blb1* and *Rpi-blb2* genes. *Avr2*, by interacting with members of the BRI1-suppressor 1-like family proteins (BSL1, BSL2 and BSL3) from potato, inhibits the activity of the oomycete infestin 1 (INF1); as a result, programmed cell death does not occur (Turnbull *et al.* 2019). *Avr3* inactivates the host ubiquitin E3 ligase CMPG1, leading to programmed cell death inhibition (Bos *et al.* 2010). Durable resistance can also be conferred by PAMP triggered immunity or non-host resistance gene. Effectors like SFI2, SFI3 and SFI4 (suppressors of the Flg22-induced immune response) play a crucial role in the early stages of invasion. *Rpi* genes recognizing such effectors provide long-term resistance. *Rpi-amr1* from *S. americanum* which is also present in the non-host *S. nigram* confers broad-spectrum resistance in cultivated potato. *Rpi-amr1* not only recognizes the effector *Avramr1* from *P. infestans* but also the *Avramr1* homologues from *P. parasitica* and *P. cactorum*. Likewise, recognition of *Avramr3* by *Rpi-amr3* from *S. americanum* activates resistance against not only *P. infestans* but also against other economically important *Phytophthora* pathogens, including *P. parasitica* and *P. palmivora*. It indicated that *Rpi-amr1* and *Rpi-amr3* provide non-host type resistance to multiple *Phytophthora* pathogens in *S. americanum*.

In India, targeted breeding for development of disease resistant potato cultivars could be undertaken only after standardization of “Seed Plot Technique” in 1963 that enabled clonal

selection for several generations without viral degeneration in plains. Iinitially late blight resistant cultivars were developed possessing race-specific *R* genes. The cultivar Kufri Jyoti released in the year 1968 possessed three dominant *R* genes, i.e. *R3*, *R4* and *R7* from *S. demissum*. Though the cultivar became the most popular potato variety throughout India after its release, its resistance soon broke down due to emergence of matching virulent races of *P. infestans* (*Avr 3, 4* and *7*). With the failure of *R* genes to provide durable resistance, attention was shifted towards durable or horizontal resistance (field resistance), controlled by many minor genes/QTLs. At ICAR-CPRI, Shimla, breeding for field resistance was initiated using *S. verrucossum* in the year 1975 with *S. phureja* acting as a bridge species to enhance crossability. Parental lines sharing gene pool from wild and semi-cultivated *Solanum species* like *S. acaule, S. demissum, S. chacoence, S. hougassi, S. microdontum,* and *S. stoloniferum,* were developed. Several late blight resistant varieties were developed for different regions that included Kufri Jyoti, Kufri Naveen, Kufri Muthu, Kufri Khasigaro, Kufri Jeevan, Kufri Neela and most of the present-day varieties like Kufri Sutlej, Kufri Jawahar, Kufri Anand, Kufri Chipsona I, Kufri Chipsona III, Kufri Lalit for the plains and Kufri Megha, Kufri Himalini, Kufri Swarna, Kufri Neelima and Kufri Girdhari for the hills. Recently, durable sources of late blight resistance available in sexually incompatible species like *S. etuberosum*, *S. pinnatisectum*, *S. cardiophyllum* have also been utilized through somatic hybridization (Chandel *et al.* 2015; Luthra *et al.* 2016; Tiwari *et al.* 2018; Luthra *et al.* 2018).

BIOTECHNOLOGICAL APPROACHES

Biotechnology has provided new opportunities for development of late blight resistant varieties. Tissue culture techniques, marker assisted selection, development of transgenics/cisgenics, genome/gene editing, and gene silencing are some of the methods being adopted worldwide to manage late blight. The research on resistance to late blight in recent years has been focused on stacking of several *R* genes in one cultivar/genotype using marker assisted selection (MAS) which might increase both durability and level of resistance. Stacking of two *R* genes has been reported to improve durability of late blight resistance, besides delaying the onset of late blight disease. The additive effect of pyramiding two resistance genes *Rpi-mcd1* and *Rpi-ber* was studied by introgression in diploid *S. tuberosum* population. Sarpo Mira with at least five reported *R* genes (*3a, 3b, 4, Smira1, 2*) is one of the few potato cultivars, developed through marker assisted breeding, which expresses significant levels of durable late blight resistance (Kim *et al.,* 2012). In India, parental lines selected through genotyping of indigenous and exotic potato germplasm collection through molecular markers tightly linked to *R1*, *R2* and *R3* genes are being utilized for pyramiding these genes in single potato host background for providing enhanced durable late blight resistance. Amplified Fragment Length Polymorphism (AFLP), Simple Sequence Repeats (SSR) markers have been used for the development of molecular map of the diploid wild species *S. chacoense* and identification of major QTLs for late blight resistance (Chakrabarti *et al.* 2014). Transgenic approach also is being adopted to complement conventional breeding. A race non-specific major gene (*RB*) from wild potato species *S. bulbocastanum* conferring durable resistance to late blight was cloned by Song *et al*. (2003) using a map-based approach in combination with a long-range PCR strategy. The transgenic Katahdin plants encoding the *RB* gene showed good level of resistance to *P. infestans*. In India, one *RB*-transgenic event of the cv. Katahdin (SP951) was received from the University of Wisconsin under ICAR–ABSP-II collaborative project and was used for introgression of the *RB* gene in the background of most popular Indian cultivar Kufri Jyoti. Several promising F1 hybrids of Kufri Jyoti x SP951 have been identified possessing high level of late blight resistance (Shandil *et al*. 2017). The level of resistance owning to the RB gene also varied with the host's genetic background (Sundresha *et al.* 2018). In another attempts, transgenic lines of cultivar Fortuna have been developed using two resistance genes *viz.*, *Rpi-blb1* and *Rpi-blb2* from *S. bulbocastanum* (Vleeshouwers *et al.* 2011). Transgenic potatoes with multiple *R* genes for late blight have also been developed by stable transformation incorporating high resistance to late blight without affecting the yield and other agronomic characters. For example, Ghislain *et*

al. (2019) reported the transfer of 3 *Rpi* genes from wild relatives (*RB, Rpi-blb2* from *S. bulbocastanum* and *Rpi-vnt1.1* from *S. venturii*) into susceptible potato varieties Desiree and Victoria. Thirteen transgenic events so produced had complete resistance to late blight in the field over several seasons in Sub-Saharan Africa where only A1 mating type is present.

RNAi is a post-transcriptional gene silencing process that downregulates the expression of target gene(s) in a precise manner without affecting the expression of other genes. In this process, a DNA construct is introduced into a cell which produces dsRNA complementary to the gene(s) of interest, which is cleaved into siRNAs by a ribonuclease called DICER or Dicer-like enzyme. RNAi strategy has been exploited to silence susceptibility genes that is considered as an alternative breeding strategy for obtaining durable broad-spectrum resistance and could be potentially applied in potatoes (Pavan *et al.* 2009; Sun *et al.* 2016). Since RNAi does not always result in a complete knockout, genome-editing could potentially be used to simultaneously knockout genes belonging to the *S*-locus for late blight susceptibility in potatoes. Van den Hoogen and Govers (2018) targeted *Avr1*, *PiTubA2,* and *PiAP5* using CRISPR/Cas9 editing system for resistance to *P. infestans* as previously demonstrated for *P. sojae* by Ma *et al.* (2017). An alternate approach of base substitution for conversion of late blight susceptible cultivar to resistant was demonstrated in Russet Burbank cultivar (Hegde *et al.* 2021). The gene encoding caffeoyl-CoA O-methyltransferase (*StCCo-AOM*T), which methylates caffeoyl-CoA to feruloyl-CoA and 5- hydroxyferuloyl-CoA to sinapoyl-CoA was selected as the candidate for gene editing. They carried out a precise single nucleotide polymorphism (SNP) mutation correction of the *StCCoAOMT* gene in Russet Burbank potato using Geminivirus-replicon based CRISPR-Cas9 mediated homology-directed repair (HDR). Recently, tetra-allelic deletion mutants were generated to knockout the function of susceptibility genes, *StDND1*, *StCHL1,* and DMG400000582 (*StDMR6-1*) using a CRISPR/Cas9 system, which resulted in increased resistance to late blight (Kieu *et al.* 2021).

The RNAi technology can also be used to target avirulence genes of *P. infestans*. Usually, plants use extracellular vesicles to deliver small RNA agents or their precursors to the pathogen. The use of small RNA transfer from host plants to the pathogen with subsequent intervention in its RNA interference pathways has been termed host induced gene silencing (HIGS). In India, this technology of silencing pathogen effector *via* expression of hairpin constructs in the host plant was exploited to silence *P. infestans Avr3a* gene for developing late blight resistant transgenics (Thakur *et al.,* 2015). However, only moderate level of resistance could be achieved by silencing a single effector. Silencing of multiple genes encoding effector/housekeeping activities were attempted later. Similarly, spray induced gene silencing (SIGS) can also be achieved using dsRNA formulation. SIGS utilizes RNA delivery into the plant from outside through the leaves and roots. An aqueous solution of dsRNA, hpRNA, or even siRNA created *in vitro* is applied by spraying on plant leaf surfaces, by inoculation/injection in the plants, or through the root system. Five genes (*SDH*, *EF-1á*, *GPI-HAM344*, *PLD-3*, and *HSP-90*) unique to sporulation, early-stage infection, and metabolism based on our microarray expression data were targeted. Efficacy of dsRNAs were evaluated by culture bioassay, detached leaf assay, and spray methods. The dsRNA with nano-clay sprayed plants showed enhanced disease resistance (4% disease severity) and least sporulation, compared to naked dsRNA spray (Sundaresha *et al.* 2021).

CONCLUSION

Potato is among the most important food crops which has a pivotal role to play in global food and nutritional security in the foreseeable future. However, yield and quality of this crop is seriously affected by a myriad of insect pests, fungi, bacterial, viruses and nematode pathogens. Amongst them, potato late blight continues to be the most important which can cause loses worth billions of dollars annually. The adverse impact of climate change further aggravates the situation both for the crop as well as the pathogen. Moreover, the risk of the spread of invasive organisms of quarantine significance has increased many folds due to liberalization of

international trade and exchange of germplasm. On the other hand, science-based strategies for management of late blight have come a long way, and several innovative approaches are being adopted for diagnostics and detection, monitoring and forecasting and management of various pest and diseases. Though fungicides still play a major role in management of late blight, deployment of resistant varieties offer the most eco-friendly and safe approach for late blight control. However, it is necessary to continuously refine and innovate breeding strategies for developing late blight resistant varieties based on classical or modern breeding approaches. Originally potato cultivars have been bred using resistance genes (*R*/*Rpi* genes) that originate from wild relatives of potato. Such programmes were initiated about 100 years ago, but the process is complex and long. Co-evolution of potato with *P. infestans* ensured abundant availability of resistance genes in the population of cultivated as well as wild potato species. Therefore, the search for and introgression of new resistant genes should be a continuous process in breeding potato for resistance to late blight.

Access to modern recombinant DNA tools like molecular mapping, positional cloning, PCR-based cloning, and genome sequencing hastened the process of *R/Rpi* gene discovery and their application in development of resistant varieties during the new millennium. Development of genetic engineering techniques has also enabled direct transfer of resistance genes from potato wild species to cultivars and easier pyramiding of multiple *Rpi* genes, which potentially increases the durability and spectrum of potato resistance to rapidly evolving *P. infestans* strains. There is need for pre-emptive or anticipatory breeding where in hybrids with more and more new resistant genes from diverse sources are produced and kept ready in advance to counter the likely emergence of new virulent races of *P. infestans* genome. Since evolution of the host's *Rpi* genes is much slower than the *P. infestans Avr* genes, it will be highly remunerative if a molecular strategy can be worked out to expedite quick evolution of *Rpi* genes governing late blight resistance needs. The existing *Rpi* genes may be made transposon rich so that these mutate at their own to resist to new *Avr* effectors of *P. infestans*. The use of *Rpi* genes recognizing conservative, essential effectors of *P. infestans* and the construction of *Rpi* gene pyramids may help to achieve durable, broad-spectrum late blight resistance, which could be accelerated through genetic engineering. Deployment of transgenic potato, however, is marred by unnecessary food safety concerns and the technology will not be available for large scale use in near future. The problem can be circumvented by applying recent gene/genome editing tools, particularly based on SDN1 and SDN2 procedures. The most advanced and selective methods aimed at precise regulation of gene function with the help of RNA interference have not yet seen wide application in agriculture due to their high cost and legal prohibitions. However, they are very promising from an ecological point of view due to their high degree of selectivity and, as a result, environmental safety.

A close collaboration between specialists in the fields of plant pathology, epidemiology, population genetics/molecular ecology, *P. infestans* molecular biology and plant breeding are advocated to enable sustainable management of a perpetual problem like potato late blight. With increasing environmental and economic pressure to reduce agrochemical inputs, future sustainable management strategies ought to place more emphasis on host resistance (natural or 'engineered'). Their success will, however, hinge on understanding current diversity and predicting future responses of *P. infestans* populations to such resistance deployment.

DECLARATION

Conflict of Interest. Author declares no conflict of interest.

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