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Harnessing Eco-Evolutionary Dynamics of Xanthomonads on Tomato and Pepper to Tackle New Problems of an Old Disease

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Abstract

Bacterial spot is an endemic seedborne disease responsible for recurring outbreaks on tomato and pepper around the world. The disease is caused by four diverse species, *Xanthomonas gardneri*, *Xanthomonas euvesicatoria*, *Xanthomonas perforans*, and *Xanthomonas vesicatoria*. There are no commercially available disease-resistant tomato varieties, and the disease is managed by chemical/biological control options, although these have not reduced the incidence of outbreaks. The disease on peppers is managed by disease-resistant cultivars that are effective against *X. euvesicatoria* but not *X. gardneri*. A significant shift in composition and prevalence of different species and races of the pathogen has occurred over the past century. Here, I attempt to review ecological and evolutionary processes associated with the population dynamics leading to disease emergence and spread. The goal of this review is to integrate the knowledge on population genomics and molecular plant–microbe interactions for this pathosystem to tailor disease management strategies.

INTRODUCTION

Race: determined by presence/absence of avirulence genes in pathogens that get recognized/evade recognition by the corresponding *R*-gene product in the host plant

Bacterial leaf spot (BLS) caused by four phylogenetically diverse *Xanthomonas* species has been a recurring problem in all tomato- and pepper-growing regions around the world since its first identification more than a century ago (27, 33). The variation in BLS strains was evident as early as the 1920s, as noted by differences in amylolytic activity. Strain host specificity toward tomato/pepper was also observed in the 1940s. *Pseudomonas gardneri*, referred to as a synonym of *Xanthomonas gardneri* (*Xg*), was identified in 1957. Determinative tests and later DNA:rRNA hybridization and rep-PCR (repetitive element palindromic polymerase chain reaction) polymorphism studies were used in the following years to survey pathogen populations around the world, and two genetically distinct groups of strains (113, 124, 125), that we know today as *Xanthomonas euvesicatoria* (*Xeu*) and *Xanthomonas vesicatoria* (*Xv*), were dominant. Reclassification based on the polyphasic approach led to taxonomic recognition of four species, *Xeu*, *Xanthomonas perforans* (*Xp*), *Xv*, and *Xg* (54). 16S rRNA analysis, a multilocus sequencing analysis (MLSA) approach, and, recently, core genome phylogenies have confirmed that *Xg* and *Xv* are phylogenetically distant separate clades [the genomic distance to *Xeu/Xp* is relatively large with an ANI (average nucleotide identity) of 88%], and *Xeu* and *Xp* are closely related sister species (93). The taxonomy continued to change for this species complex with researchers combining or splitting species. For example, based on ANI, *Xeu* and *Xp* could be considered a single species (11). *Xg* has been recently reclassified as *Xanthomonas hortorum* pv. *gardneri* (81). I refer to them as four species, *Xeu*, *Xp*, *Xv*, and *Xg*, in this review to be consistent with the reference genome designations.

Over the past century, there have been significant shifts in species and race associated with outbreaks. Until the 1990s, *Xeu* and *Xv* were dominant around the world, although regional specialization of each species was observed. Since its first description by Šutic in 1957 in Yugoslavia, *Xg* was first identified in Costa Rica in 1999 (55). Tomato production across different continents experienced a pathogen species shift with the introduction of the new species, *Xp*, in 1991, followed by its clonal expansion and diversification over time, regional differentiation in *Xv*, and the global spread of a single MLSA haplotype of *Xg* (120). Race shifts have been observed in *Xeu* population in pepper production, as well as the recent emergence of *Xp* on pepper. Population genetics and genomics studies have revolutionized the research into the ecological and evolutionary drivers responsible for the divergence of *Xp* lineages and the race shift of *Xeu*. Molecular plant–microbe interactions and whole-genome comparison studies have identified emerging virulence factors associated with these shifts. The goal of this review is to apply ecological and evolutionary frameworks to investigate these population shifts and harness this knowledge to guide disease management strategies.

Race Structure of Bacterial Leaf Spot Xanthomonads

BLS xanthomonads display a race structure, the designation for which depends on the host reaction of specific tomato/pepper genotypes that carry resistance genes. There are 5 races on tomato accessions, and at least 11 races on pepper, P0–P10 (114). The relationship between race/host range and species assignment is not straightforward. Some strains are pathogenic on both tomato and pepper, and others are pathogenic on only one host. T1 strains typically are *Xeu*. T2 strains are infectious to all three resistant tomato genotypes and typically are *Xv* or *Xg*, and T3–T5 correspond to *Xp* (119).

Shift in Species Distribution and Prevalence on Tomato

Xp was isolated in 1991 in Florida and 1993 in Mexico from tomato fields in which a relatively homogeneous population of *Xeu* was dominant (17, 74, 113). These *Xp* T3 strains may have been

via introduced infected hybrid seeds or seedlings produced in Southeast Asian countries and widely distributed (52). *Xp* then slowly replaced *Xeu* in tomato fields, gaining dominance. A race shift from T3 to T4 strains, followed by the dominance of T4, was later observed in 2006 and 2011 surveys in the southeastern United States, and a recent survey indicated that only 8% of all strains were T3 strains (64). *Xp* strains have diverged into at least six lineages based on core genome phylogeny (83, 84, 106, 122).

In the north-central tomato production region of North America, diverse *Xv* lineages were dominant on tomato in the late 1990s (74). A species shift appeared to have occurred with the first report of *Xg* as an emerging pathogen on tomato in 2009–2010 (75) and the dominance of *Xp* T4 strains over the past decade (30). Interestingly, *Xg* dominated *Xp* in the northern tomato production areas in Michigan and Canada (24). These surveys also identified *Pseudomonas syringae* pv. *tomato* strains lacking toxins from infected tomato fields. Interestingly, *Xg* strains from Ontario had identical rep-PCR fingerprints to those from *Xg* strains from Yugoslavia and Costa Rica, indicating the role of global seed movement in recent geographic expansion (120). *Xg* has caused recurring outbreaks in northeastern US tomato fields since 2001 (63).

Xp and *Xg* have gained dominance over the past two decades in Brazil, with declining *Xeu* populations since early 2000. Between 1997 and 2005, increased occurrences of *Xp* and *Xg* outbreaks were associated with imported tomato hybrid varieties in Brazil and coincided with an increased tomato production in a new area of Brazil and the gradual substitution of open-pollinated cultivars (either locally bred or imported from California) with hybrid seeds marketed by international seed companies (95). *Xg* strains were mostly isolated from the fresh market tomato fields in regions of high altitude (5). *Xp* replaced *Xeu* and *Xv* in Taiwan and Korea in 2010, where a slow shift from dominant *Xeu* to *Xp* was observed in the decade prior (18). *Xg* was first reported in Malaysia in 2013 (97) but has not yet been reported anywhere else in Asia.

Regional specialization has been observed in tomato fields in other parts of the world, with *Xv* still lingering in some parts of the world, albeit at low frequency. *Xv* was the only species infecting tomato in the late 1990s in the Indian Ocean region, but all four species were identified in 2010 on tomato and pepper, with *Xeu* being prevalent (40). Although no marked intraspecific variation was detected in *Xp*, *Xv*, and *Xg*, a recombinant lineage of *Xeu* was detected. In Russia, both *Xg* and *Xv* strains were recovered from infected tomatoes in 2006 (65). Interestingly, this study also identified strains from 1947–1949 as *Xv* and *Xg*, indicating the presence of *Xg* earlier than its first description in Yugoslavia in 1957. All three species (*Xp* T3, *Xg*, and *Xv*) were identified in Africa, with some atypical *Xeu* and *Xp* strains in Nigeria (46–48) and two haplotypes of *Xv* in Ethiopia (57). The presence of at least two BLS species, *Xv* and *Xp*, was reported on tomato in Australia (99). The majority of these *Xp* strains from Australia were closely related to the Florida lineage but formed a distinct clade. One strain belonged to a novel lineage from Alabama, and another belonged to the lineage found in both Alabama and Florida (E. Newberry & N. Potnis, unpublished data). The presence of multiple species on tomato in various parts of the world may have been due to the importation of seeds or plant material from multiple sources (40).

Race Shift on Pepper

Xeu has been a dominant pathogen on pepper around the world for the past century, with genetically homogeneous populations (74, 120, 130). Despite highly clonal populations, the presence of at least 11 races has been observed. Pepper race 2 (P2) strains dominated in Florida until 1982 (22), but then a sudden shift to a prevalence of P1 strains was reported following their introduction, possibly via infested seeds (91). Interestingly, this race shift was not a result of selection pressure from the host but rather the higher fitness of P1 strains compared to P2 strains. P1 strains not

only displayed greater virulence compared to P2 (87) but also showed increased survival in soil and dead plant material (86), thus providing them an overall competitive advantage (25). This race shift involved the loss of avirulence (plasmid-borne *avrBs1* gene), not via loss of a plasmid but rather a mutation, the spontaneous insertion of the IS476 element, in *avrBs1*. This indicated the significance of this mutated version of the gene in survival outside a living host. The longer persistence of the mutant P1 created a higher chance of establishing contact with the host and thus its prevalence in successive seasons.

With the increasing prevalence of P1 and P2, a *Bs2*-resistant bell pepper variety was released in 1984. Although this resistant variety was planted sporadically, a *Bs2*-resistant commercial variety with acceptable horticultural traits was deployed in the 1990s, and by 2000 nearly all commercial bell pepper cultivars contained the *Bs2* gene. The first field strains to overcome *Bs2* were identified in 1993, with these strains gaining dominance (50% mutant *avrBs2* alleles) in *Bs2* pepper fields by 1999; thus, the effectiveness of this resistance gene was seen in the field for only six years (66, 67). Pepper races capable of overcoming *Bs2*, i.e., P4, P5, and P6, were also responsible for bacterial spot of *Capsicum chinense* (hot pepper) in Barbados. It is thought that these races were introduced to bell pepper and tomato via bacterial spot–infected *C. chinense* in 1993 because *C. chinense* was grown in rotation with bell pepper and tomato (38). Among *avrBs2* mutant alleles observed in the pepper strains isolated during 1969–2001, a large transposon insertion, frameshifting insertion/deletion, and single amino acid changes (R403P or A410D) were found (130), the most common of which was a change in the repeat structure of the 5-bp CGCGC repeat, possibly due to polymerase slippage during replication (35, 117, 130). This 5-nt deletion in *avrBs2* led to a loss of resistance in *Bs2* pepper plants and abolition of *avrBs2*-mediated enhancement of fitness on susceptible plants. Point mutations such as a G to C transversion at location 1386 in *avrBs2* lead to the retention of virulence but enabled evasion of recognition by *Bs2* (35). Thus, *avrBs2* alleles evolved to decrease detection by *Bs2* while maintaining their virulence function, consistent with an evolutionary arms race model (130). The fact that 50% of the pathogen population still carried the wild-type *avrBs2* allele indicated that *avrBs2* was selectively favored in some situations and the total loss of *avrBs2* may not have been a suitable evolutionary strategy of the pathogen in responding to this selection pressure. Thus, *Bs2* is still considered an important resistance gene against BLS in pepper breeding programs. Continued surveillance of *avrBs2* alleles indicated that *avrBs2* is a conserved effector in *Xanthomonas* populations and the same abovementioned allelic variants of *avrBs2* were observed over the past two decades with no new emerging variants.

P6 strains (which are pathogenic on plants containing the *Bs1*, *Bs2*, and *Bs3* resistance genes) have been responsible for continued outbreaks over the years since their first report in the Upper Midwest of the United States in 1993–1994 (102) and in Florida in 1997–1998 (90). With the prevalence of P6 on pepper and its ability to overcome all three resistance genes in pepper, the recessive resistance genes *bs5/bs6*, which provide effective and additive quantitative resistance against P6, were incorporated into the breeding programs for hybrid commercial pepper cultivars by Seminis. These commercial bell pepper varieties (Seminis X10R®) are now available and are widely used by growers (114). These resistant cultivars that carry recessive resistance genes appear to limit BLS disease severity; however, epiphytic populations of *Xanthomonas* can be recovered from these varieties, causing occasional water-soaking symptoms, especially when susceptible varieties of specialty peppers are planted in the same field (N. Potnis & B. Dutta, unpublished data).

Although *Xeu* continues to be predominant on pepper around the world (8, 18, 40, 83, 99, 106, 120), *Xp* has been recently isolated from infected pepper, suggesting possible host range expansion of *Xp* on pepper (84, 106). The presence of pathogenic *Xg* on pepper and its recent global incidence is concerning (120) because strains of *Xg* can cause disease on recessive resistant varieties. *Xg* is not yet found in the southeastern United States. However, recent findings of pepper-pathogenic

Xp strains carrying a plasmid identical to that in *Xg* (84) warrant enhanced disease surveillance of pepper varieties in the southeastern United States.

Four Species Have Converged to Cause Disease on a Common Host, Tomato

Latent infection period: referring to the period from the time of infection to symptom expression

Although four species cause bacterial spot disease symptoms on tomato, they differ in overall aggressiveness as measured by two traits, latent infection period and disease severity (88). *Xg* is the most aggressive (shorter latent infection period and higher disease severity) among the four species at 25°C (5, 7, 92). The four species differ in the presence/absence of various secretion systems and associated effectors (93). Given the observation of differences in latent infection period, it is possible that although BLS species utilize similar strategies to suppress host immune responses, the four species might differ in the strategies that determine successful epiphytic and endophytic colonization during the initial stages of infection. Because the type III secretion system is an important pathogenicity factor in xanthomonads, it can be assumed that core type III effectors account for a common infection strategy that has allowed them to evolve to converge on a common host. These core effector genes include *avrBs2*, *xopD*, *xopF1*, *xopK*, *xopL*, *xopN*, *xopQ*, *xopR*, *xopX*, and *xopZ*, although some effectors show positional rearrangement or sequence divergence in *Xv/Xg*, as indicated by lower sequence identity (~88% or lower). Among these core effectors, XopN (58), XopD (59, 60), XopX (115), XopL (109), and XopQ (118) have been studied for their role in overall disease development and suppressing PAMP-triggered immunity or effector-triggered immunity. The differences in effector repertoires among four species can explain differences in the disease severities displayed by the four diverse species; however, the contribution of the unique effectors of each of these species to the infection process largely remains to be investigated.

ECOLOGICAL DRIVERS OF DISEASE OUTBREAKS AND ASSOCIATED EVOLUTIONARY PROCESSES

BLS is an endemic seedborne disease. Although infested seeds have been thought to be a major source of inoculum, we also need to consider the relative contribution of other factors such as alternate host/volunteer plants, climate, inoculum sources, host genotype, and modern agricultural practices that can contribute toward overall disease severity and influence pathogen infectivity, which thus requires us to reconsider the disease pyramid (**Figure 1**).

Tracing Back the Origins

A fundamental question related to pathogen ecology and evolution is how today's host-specialized pathogenic species have emerged. Reconstruction of the clonal genealogy of the strains collected over the span of several decades has allowed researchers to develop a model to explain the evolutionary history of pathogens (79, 80, 130). The most-recent common ancestors (MRCAs) of today's host-specialized pathogens presumably had a wider host range consisting of diverse plant hosts with generalist lifestyles and existed before the domestication of crop plants and the advent of agriculture (79, 127). Genomic fingerprinting–based methods for classifying *Xanthomonas* strains revealed a genetically heterogeneous *Xanthomonas axonopodis* species complex containing subgroups 9.1–9.6 that collectively displayed a broader host range, but each strain showed a narrow host range. Of these subgroups, *Xeu* and *Xp* belong to a 9.2 group (96). A clonal genealogy reconstruction showed that generalists diverged during the last 25,000 years and ecology-driven specialization of these subgroups occurred during the past two centuries (79). A population bottleneck for the 9.2 *X. axonopodis* group may have occurred between approximately 1940 and 1960. Large-scale modern agriculture changes such as large-scale intensified monoculture in the twentieth century made such susceptible crop hosts more available and led to the emergence of the founder strains.

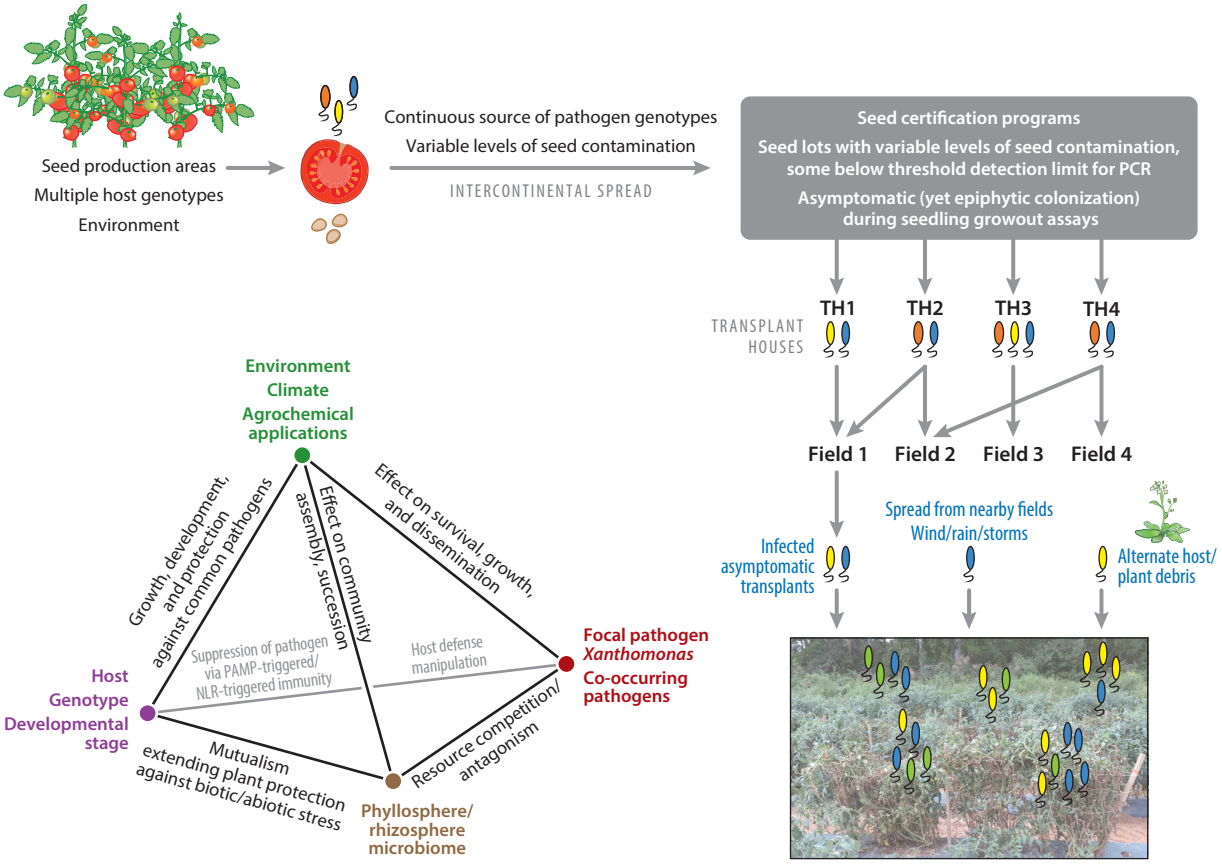

Figure 1

Ecological and epidemiological processes influencing bacterial leaf spot outbreaks around the world. At each step during the production chain, from seed production fields to the fruit production fields, several factors described in the disease pyramid can influence the overall success of the pathogen. Along with co-occurring microbes, the presence of multiple pathogen genotypes at each of the steps during the production chain can influence overall disease severity as well as increase chances of recombination and horizontal gene transfer, leading to the emergence of new variants of bacterial spot xanthomonads. These pathogen variants encounter competition among each other and from the resident flora as well as selection pressure from the host defense system and environment. Abbreviations: NLR, nucleotide-binding leucine-rich repeat; PAMP, pathogen-associated molecular pattern; PCR, polymerase chain reaction.

Agricultural advances and globalization contributed to the recent migration events in which some strains were selected and disseminated. Modern agriculture further provided opportunities for overlapping ecological niches that led to exchanges of host-specialization genes, giving rise to distinct pathovars. Similar analysis of a more homogeneous population of *Xeu* showing extremely low genetic diversity estimated that the MRCA of the modern *Xeu* population occurred 28–1,400 years ago (assuming 50–500 bacterial generations per year), which coincided with the timeline of domestication and modern agricultural practices (130). The two other species, *Xv* and *Xg*, are distantly related to the 9.2 *X. axonopodis* group (containing *Xeu* and *Xp*) yet display pathological convergence on tomato and pepper. It is possible that *Xv*/*Xg* has undergone host-associated specialization independently of *Xeu*/*Xp*.

Vinatzer and colleagues' work with environmental and crop-associated pseudomonads indicated that today's pathogens emerged from generalist populations in multiple independent

events (80). Unlike *Pseudomonas*, populations of xanthomonads associated with rainwater or nonagricultural environments have not been extensively studied. The isolation of xanthomonads from rainwater by Vinatzer and colleagues and their phylogenetic diversity within *Xanthomonas* could indicate the presence of environmental *Xanthomonas* populations that need to be considered to understand the emergence of plant-pathogenic xanthomonads (M. Pena, N. Potnis, B. Vinatzer, unpublished data). Whether these rainwater isolates are commensals or even weak pathogens remains to be determined. Interestingly, commensalistic/opportunistic xanthomonads have been identified to be associated with infected tomato and pepper transplants or field plants (37, 126). Genomic comparisons showed that commensal strains isolated from different crop plants belong to different clades within *Xanthomonas*, with some in the *Xeu* species complex group, and differ in their repertoires of secretion systems and associated factors (M. Pena, N. Potnis, J. Jones, M-A. Jacques, unpublished data). Assessing the contribution of differential virulence factor repertoires in diverse commensals can provide clues to their generalist nature. BLS xanthomonads may also inhabit/infect wild solanaceous plants (51, 99, 126). Exploring *Xanthomonas* isolates from wild solanaceous plants and comparing their patterns of genetic diversity with that from strains from cultivated crops might be crucial to deciphering the stabilized evolutionary patterns in natural ecosystems.

International Seed Trade and Regional Transplant Movement Responsible for Introduction of New Species or Races

BLS *Xanthomonas* is a seedborne pathogen, and thus contaminated commercial hybrid seeds are an efficient vehicle for the intercontinental transfer of novel pathogenic species or races and have likely affected the distribution of these species. Were the new lineages emerging in *Xp* populations first introduced via infested seeds? Or are they the result of independent local adaptation in different geographical areas? Core genome phylogenies and single nucleotide polymorphism (SNP) tracking can provide clues to this question. The regional movement of seedborne phytopathogens can also occur on transplants, as many transplant operations supply seedlings for use out-of-state and internationally. The use of overhead irrigation during transplant production can generate aerosols that can allow the rapid movement of *Xanthomonas*. Pathogens can establish asymptomatic epiphytic populations on transplant seedlings, thus making rouging of symptomatic transplants an ineffective disease management strategy (1, 3).

To what extent do the infested seeds pose phytosanitary risks? We have a limited understanding of the threshold pathogen population present on the leaves, stems, or blossoms in the seed production fields necessary for seed infestation, the effect of seed sanitation practices on pathogen load, and the threshold necessary for effective seed-to-seedling transmission of the pathogen. BLS pathogen seed contamination can occur via penetration of fruit lenticels or blossom colonization (28). Epiphytic populations build up during the growing season, not only on the leaves but also on buds and blossoms (up to as many as 10^4 cells per g fresh weight of bud under conducive environmental conditions), regardless of host resistance to the pathogen (89). By artificially inoculating blossoms using the *Xeu* pathogen, Dutta et al. (28) showed that levels as low as 10 cells/blossom can result in the infestation of 14.3% of the seed lots. Thus, it is important to be vigilant for asymptomatic epiphytic colonization of pathogens, especially during the production of seeds of different cultivars, including resistant ones. The nonuniform distribution of pathogens within seed lots also presents challenges for seed certification programs. Of course, climatic conditions play a major role in plant-to-seed and seed-to-plant transmission and subsequent disease outbreaks. A study in which plant-to-seed and seed-to-plant transmission were assessed with different starting inoculum levels of *Xeu* and *Xv* in the pepper and tomato production fields in Italy and Serbia

showed that 1.5–3.17% of the pepper seed lots were contaminated by *Xeu*. However, when these infested seed lots were planted in the second cropping season, no bacterial spot symptoms were observed on the plants, nor did seeds extracted from this second season contain any detectable level of pathogen. Agronomic practices might also play an important role in determining the threshold number of pathogen cells on seeds needed for subsequent disease on the crop (36). Commercial seeds are routinely treated to reduce surface microbial contaminants. Understanding the effect of pathogen survival on seed treatments and the effect of seed preparation processes such as pelleting and priming on the efficacy of seed treatments and the threshold seed population sizes needed for disease can be crucial to mitigating disease outbreaks.

Local Adaptation of Pathogen Races/Species Upon Introduction into a New Geographical Location

Upon introduction of a new species or new lineage, pathogens can adapt in response to the selection pressure imposed by biotic and abiotic factors present in the local environment. Population genomics and metagenomics studies have helped us to understand these patterns and mechanisms of local adaptation and have uncovered the genetic factors responsible for higher pathogen fitness in the local environment as described below.

How did *Xanthomonas perforans* manage to take over and eventually replace populations of other species on tomato? The invasion of *Xp* into tomato fields where previously only *Xeu* or *Xv* existed suggests that these species coexisted at different temporal and spatial scales but also responded to the interactions with the host, other resident microflora, and abiotic factors as well as to each other. In Florida tomato fields, *Xp* strains had a competitive advantage over *Xeu*, and the species displacement of *Xeu* by *Xp* was at least in part due to its production of three bacteriocins, BcnA, BcnB, and BcnC, that are effective against *Xeu* (41, 53, 123). BcnA, which is particularly toxic to *Xeu*, is an Rhs family toxin containing Rhs repeats and is encoded in a locus with five open reading frames, of which one is an immunity protein. BcnB and BcnC are proteases (77). Such interspecies interactions mediated by bacteriocins might be one explanation for how *Xp* replaced *Xeu*, as a relatively low number of *Xeu* strains were isolated from infected tomato in the following years and none after approximately a decade. However, *Xp* replaced *Xv* in the northern region of the midwestern United States despite the fact that bacteriocins are not effective against *Xv*. Other explanations for the prevalence of *Xp* over other species could be the continued input of *Xp* into fields via contaminated seeds and, most importantly, its local adaptation. In Brazil, *Xp* is more aggressive than other BLS species at temperatures above 25°C and has a competitive advantage over them in terms of both disease severity and in planta growth at higher temperatures (7). Its adaptability to higher temperatures might have provided *Xp* a competitive advantage to prevail in the presence of *Xg*.

Factors contributing to the intraspecific heterogeneity in *Xanthomonas perforans* and its higher adaptability and competitiveness in tomato fields. Since its establishment in tomato fields around the world, *Xp* has undergone significant genetic changes. The race shift of *Xp* from T3 to T4 occurred in tomato fields before the *Xv3* resistance gene was transferred to commercial cultivars. How T4 strains emerged was a puzzle because there was no known selection pressure imposed by commercial tomato varieties, but there were grape tomato cultivars containing the *Xv3* gene, possibly originating from *Solanum pimpinellifolium*, planted in Florida. These *Xv3*-containing grape tomatoes could have imposed the selection pressure that led to an accumulation of mutations in *avrXv3* (114). T4 strains slowly gained dominance over T3 strains in Florida, and by 2012 all strains collected were T4. The T3 strains, however, appear to be re-emerging based on

recent surveys in Florida and Alabama (64, 83, 84). At least three different types of mutations seem to have occurred in T4 strains that include the absence of the *avrXv3/xopAF* effector as well as mutations disrupting the *avrXv3* effector gene, including transposon insertion, SNPs resulting in premature stop codons, and SNPs resulting in two amino acid changes within this effector (L50P and V182L) (64). T4 strains from Florida contain an approximately 1,200-bp insertion (119), and T4 strains from Brazil and Nigeria contain an 859-bp insertion containing a transposase that originated in *Xg* (5, 46), indicative of horizontal gene transfer (HGT) between *Xp* and *Xg*.

HGT: horizontal gene transfer

This race shift was also accompanied by the divergence of *Xp* into at least six lineages (84) based on the core genome phylogeny of *Xp* strains collected in the southeastern United States. The impact of recombination on nucleotide variation was greater than the impact of mutation in individual BLS species (46, 120); thus, recombination is a significant force responsible for the diversification of *Xp*. Recombination has also been referred to as a cohesive force blurring the boundaries between *Xeu* and *Xp*, resulting in some atypical recombinant strains of *Xeu* and *Xp* (11, 46). These two sister species have frequently exchanged genes through recombination, and recombinant variants have arisen over time that have subsequently acquired additional fitness factors that offer them significant advantages over the other variants in successfully infecting tomato or pepper (**Figure 2**). The two dominant *Xp* lineages in Florida, which contain recombination patterns originating in *Xeu*, have also lost their ability to produce the bacteriocin active against *Xeu*. Although recombination signatures are indirect proof of overlapping ecological niches, *Xeu* has not been isolated for approximately a decade according to recent surveys. Our recent attempt at shotgun metagenomics of phyllosphere samples successfully identified low-abundance variants of

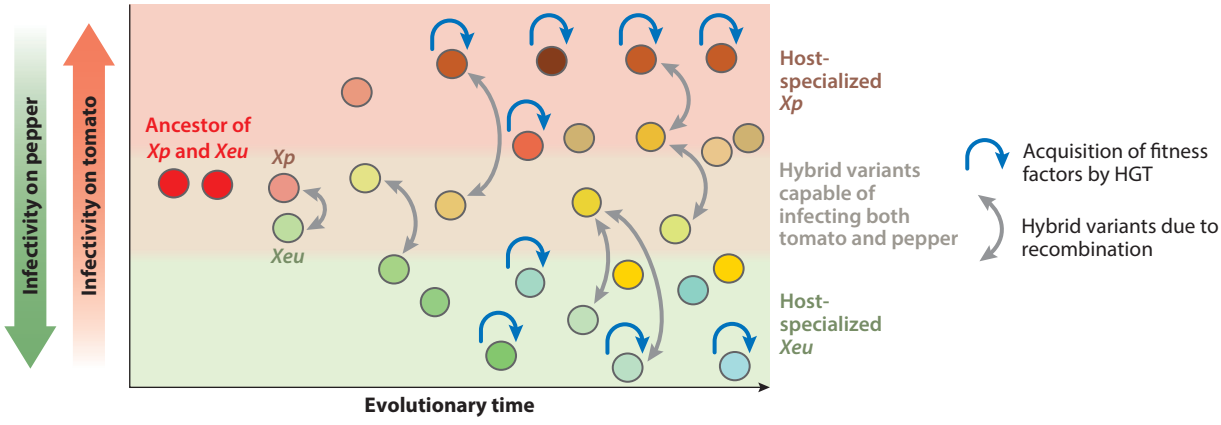

Figure 2

Hypothesized consequence of the trade-off relationship between infectivity to tomato and pepper in sister species. *Xanthomonas euvesicatoria* (*Xeu*) and *Xanthomonas perforans* (*Xp*) are sister species and very similar in genetic composition. Thus, it is safe to assume that they had a common ancestor that was pathogenic on both tomato and pepper, and the two sister species evolved over time before diverging lineages specialized onto the two hosts as a result of stepwise adaptation on respective hosts over time. Recombination has played a significant role in creating hybrid variants among these sister species (as indicated by double-headed gray arrows). The resulting recombinants have gained infectivity on either tomato or pepper, depending on the contribution of the genes to host adaptation. For example, *Xp* recombinants have been identified recently with increased infectivity on pepper but have also retained pathogenicity on tomato. Acquisition of fitness factors from other species by horizontal gene transfer has allowed them to gain fitness and competitiveness (indicated by single-headed arrows). *Xp* containing *avrBsT/xopJ6* and *Xeu* containing *avrBs4* are host-specialized lineages on tomato and pepper, respectively, because of the fitness advantage that they provide but also because these avirulence genes trigger effector-triggered immunity on the other host. Of course, the field-level dominance and infectivity of either sister species or recombinants on tomato and pepper depend on several factors, including but not limited to interspecies interactions. Abbreviation: HGT, horizontal gene transfer.

Xp but did not identify *Xeu* on tomato despite the dominance of *Xeu* on adjacent pepper plants in the same field. However, we cannot rule out the possibility that these recombinant strains emerged when *Xeu* might still have been present, even in low abundance, in tomato fields. It is also possible that the bacteriocin-mediated killing of *Xeu* fostered uptake of *Xeu* DNA by *Xp* strains, leading to the emergence of these recombinants. Interestingly, in the neighboring state of Alabama, *Xp* lineages that are dominant on tomato are novel lineages not reported in Florida and contain recombination signatures originating from closely related pathovars within the *Xeu* species complex. This is surprising because southeastern states all obtain their transplants from common transplant producers in this area. It is possible that these lineages are present at low abundance in Florida and thus not yet isolated. This suggests that these new lineages might disperse to fields where interactions with other endemic lineages, climatic conditions, susceptibility of host genotype, and/or disease management practices, depending on the production scale, might dictate the dominance of lineages in different regions in the southeastern United States. One of the novel *Xp* lineages from Alabama contains a plasmid that includes the transcription activator-like effector (TALE) *avrHah1*, which is identical to that found in *Xg*, even though *Xg* has not been reported in the southeastern United States. Another lineage contains a plasmid containing novel TALE, *pthXp1*. This effector was also found in other *Xp* strains in Florida, Africa, and Australia.

The prevalence of certain *Xp* lineages over others can be due to the fitness factors they harbor. AvrBsT (XopJ2) is a recently acquired plasmid-borne fitness factor on tomato in dominant *Xp* lineages. This effector belonging to the XopJ clade within the YopJ superfamily of effectors (128) elicits a hypersensitive response (HR) on pepper (23) but downregulates defense-related genes in tomato (61). AvrBsT has been previously reported in *Xv* isolated from tomato and older *Xeu* isolates from tomato (99). AvrBsT imparts higher transmissibility to *Xp* (2). Higher epiphytic populations in the field with the AvrBsT-carrying pathogen confer long-distance spread within local populations but also higher chances that the blossoms and developing seeds become contaminated, thus causing more vertical transmission and improving overall pathogen success (89). This could explain the dominance of *Xp* lineages containing AvrBsT in tomato fields. However, the presence of AvrBsT also means these strains are not pathogenic on pepper (**Figure 2**). Another variant of the XopJ family, named XopJ6 (70.99% identity to XopJ2), has been associated with a plasmid in a new emerging *Xp* lineage, which includes T3 strains (44). This effector has 99% identity at the nucleotide level to the effector from *Xanthomonas vasicola* pv. *arecae*, a pathogen of the Areca palm. Another important emerging effector group in *Xp* populations is the TALE effector family, which includes *avrHah1*, and *pthXp1* (84). These have also been found on a plasmid. AvrHah1 from *Xg* enhances water-soaking on tomato by promoting aqueous environments in the leaf apoplast (105). Other effectors that are also plasmid-borne and acquired by diverging *Xp* populations include *xopE2* and *xopAO*. Their contribution to virulence of *Xp* on tomato/pepper is not yet explored.

Shotgun metagenomics on phyllosphere tomato samples from bacterial spot–infected fields helped resolve intrapopulation heterogeneity and confirmed the presence of multiple lineages of *Xp* coexisting in a single small-scale grower's fields in Alabama (83). In response to the selection pressures imposed by host/environment or management practices, the pathogen might have responded through a shift in population associated with fields colonized by multiple pathogen genotypes that employ varying infection strategies via their differing repertoire of virulence factors. Although this study did not sample individual plants and thus the incidence of coinfections cannot be estimated, several studies in the 1990s revealed mixtures of multiple races associated with a lesion, with differences in lesion size caused by specific races. The presence of multiple races associated with single lesions could be responsible for the rapid and extensive shifts in pathogen races because these lesions could be active sites for the exchange of genetic information between races via HGT of different traits (38, 85, 87). Thus, resistance breeding programs need to consider

such coinfections by multiple races of pathogen, where host resistance might be compromised. It is unclear whether coinfection is always correlated with increased disease severity for BLS.

Dominance of *Xanthomonas gardneri* on tomato in cooler weather. Although *Xp* has been dominant in the majority of tomato-growing regions in tropical/subtropical climates, *Xg* has a competitive advantage in cooler climates. A shorter latent period and higher disease severity in cooler weather make *Xg* successful in these regions (7). The presence of ice-nucleation genes in *Xg* and *Xv* can offer adaptative traits in cooler climates and might also contribute to overall fitness that allows successful overwintering or allow spread via raindrops to promote long-distance movement (N. Potnis, unpublished data), similar to pseudomonads that have been shown to contribute to the water cycle. However, it is not known if *Xg/Xv* can survive in snowpack or rain. *Xg* also contains unique effectors (some of which are homologs of *Pseudomonas* effectors) not present in other BLS pathogens, such as *avrBs1* class (homolog *avrA* 79% identity), *xopAS* (*hopAS1* 41% identity), and *xopAO* (*avrRpm1* 61% identity) (93). Their role in providing a competitive advantage to *Xg* on tomato remains to be investigated.

Local adaptation of *Xanthomonas euvesicatoria* on pepper. Apart from the race shift of *Xeu* strains on pepper, *Xeu* shows a high degree of plasmid diversity (at least 20 different plasmids, with sizes ranging from 3 to 300 kb), with an unusually high number of plasmids (four or more) per strain (with 71 plasmid profiles; 19), despite an overall lack of genetic variation in the chromosome (130). This indicates that plasmids offer a potentially large source of variation in this species. Frequent transfer of plasmids has been observed among the strains even within a single growing season (19). Indeed, plasmids encode important traits in *Xeu* populations; for example, the avirulence gene *avrBs1* is linked to copper resistance on a self-transmissible plasmid (112). The presence of three plasmid-borne avirulence genes, *avrBs1*, *avrBs3*, and *avrBs4*, within individual strains is variable. Each of these avirulence proteins along with the chromosomal functionally conserved essential effector AvrBs2 had significant and additive contributions to fitness traits [as measured by transmission, symptom development, and epiphytic survival (69)] (129). Different alleles of a core effector gene, *avrBs2*, allow a pathogen to escape recognition by Bs2 but conserve its virulence function (56, 117). AvrBs1-, AvrBs3-, and AvrBs4-induced cellular changes in *Nicotiana benthamiana* have helped elucidate their contribution to virulence. AvrBs1 and AvrBs3 expression lead to an increased number of plant vesicles and enlargement of the central vacuole and cell wall. The hypertrophy induced by AvrBs3 (76) might help the egress of bacteria, thereby promoting transmission, or it could provide increased availability of apoplastic nutrients to the growing pathogen population. AvrBs4-induced formation of large catalase crystals in peroxisomes indicates suppression of plant defense by detoxifying hydrogen peroxide generated in peroxisomes during the oxidative process (39). The avirulence genes *avrBs3* and *avrBs4* are dominant in *Xeu* populations sampled within the past three decades (106). However, the prevalence of *avrBs4* in *Xeu* population also means that these strains are limited to pepper because AvrBs4 triggers the HR on tomato that carries the *Bs4* resistance gene (103) (**Figure 2**). Some of the type III effectors that are unique and conserved in *Xeu* populations (compared to *Xp*) include *xopG*, *xopB*, *xopJ*, *xopM*, and *xopS*. One such *Xeu* unique effector, XopB, suppresses cell wall–invertase activity, most likely to prevent sugar-mediated defense signals, and thus suppresses immunity in pepper (104, 111). Although these effectors have been studied for their mode of action within the host, their contributions to pathogen fitness are not yet known.

***Xanthomonas perforans* emergence on pepper.** *Xp* strains isolated in the 1990s in Florida were known to be restricted to tomato and did not have the ability to grow and infect pepper even

in the absence of *avrXv3*, which triggers HR on pepper (10). Diverse lineages of *Xp* have arisen in recent years as a result of homologous recombination derived from *Xeu* and related pathovars within the *Xeu* species complex (46, 84, 122). Among these, two separate lineages have expanded their host range to include both tomato and pepper. Horizontal transfer or a recombination event alone does not readily explain this shift in the host range of *Xp* on pepper. Genome-wide association analyses identified multiple candidates for pepper pathogenicity located in the genomic regions identified as recombination hot spots, which included TonB-dependent receptors, genes involved in amino acid transport, type II and type VI secretion systems, and cell wall–degrading enzymes (E. Newberry & N. Potnis, unpublished data). Interestingly, all these candidates were also identified previously as putative host specificity factors (dicot versus monocot preference) using genome-wide comparisons of xanthomonads across its genus-level phylogeny (16, 45). Thus, host specificity factors do not seem to be limited to type III effector repertoires but also include factors involved in the evasion of innate immune responses, sensor/chemotaxis, and specific nutritional requirements of pathogens (45). Preliminary experiments also indicated that *Xp*'s response to polygalacturonides might play a role in the adaptation of the pathogen to the pepper niche (E. Newberry & N. Potnis, unpublished data). Thus, host specificity is likely a multigenic trait. Independent evolutionary processes in different lineages might have shaped this host shift in *Xp*.

Agricultural Practices Can Influence Adaptive Potential of the Pathogen by Altering Plant–Pathogen Interactions

Routine agricultural practices employed during crop production as well as disease management practices to tackle multiple diseases during a growing season can significantly alter the outcomes of plant–pathogen interactions. Inferring the influence of individual components associated with agricultural practices on pathogen adaptation is often challenging, especially in natural settings. Below are some factors associated with crop production practices that have led to altered host susceptibility or higher fitness in BLS pathogen populations.

Choosing host cultivars. Although resistance genes were identified in tomato in response to emerging races/species in the past, virulent variants were identified before resistance lines could be commercially deployed (114). Breeding tomatoes for disease resistance against BLS *Xanthomonas* has not been successful because (*a*) resistance genes identified from wild sexually compatible species are often narrow spectrum and do not recognize genetically diverse species/lineages of the BLS *Xanthomonas* species complex and (*b*) because of the linkage of undesirable horticultural traits. One such example of linkage drag includes the majority of the currently available inbred lines/hybrids containing the *I-3* locus, which imparts resistance against Fusarium wilt race 3, a causal agent of vascular wilt disease. These *Fusarium*-resistant lines show increased susceptibility to BLS (72). Reduced bacterial spot disease severity was observed when introgression size was reduced, confirming linkage drag associated with the *I-3* locus in the majority of the tomato inbred lines and hybrid (43). Thus, choosing the currently available *Fusarium*-resistant variety might predispose tomato plants to increased disease susceptibility toward BLS.

Commercial bell pepper varieties carrying *Bs2* and *bs5/bs6* resistance against *Xeu* are available; however, many specialty peppers such as jalapeño and banana are extremely susceptible to *Xeu*. Growers often maintain several pepper types and varieties in contiguous planting during the same season because of consumer demand. When resistant *Bs2/bs5/bs6*-containing peppers and susceptible cultivars are planted in the same field, higher epiphytic populations on symptomless resistant peppers might serve as an inoculum source for neighboring susceptible pepper cultivars (70, 89).

Overuse of copper bactericides. Copper sprays supplemented with the fungicide mancozeb are used in tomato/pepper fields worldwide but are unsuccessful in controlling BLS, especially in tomato. This poor performance of copper bactericides is due to many factors, including hot humid climates that foster high epiphytic populations in protected sites such as buds where bacterial cells escape lethal doses of copper as well as a high incidence of copper tolerance among the pathogen population. Although the spread of copper resistance–conferring plasmids encoding the *copLAB* operon is prevalent in BLS xanthomonads (42), this operon, along with other heavy metal resistance genes, was also found to be part of a Tn3-like transposon system integrated into plasmids in *Xg* JS749–3 and *Xv* LM159 (98). Interestingly, the emergence of chromosomally encoded copper resistance within a genomic island has been noted during recent genome analyses in Florida (R. Bhandari, S. Bibi, J. Jones, N. Potnis, unpublished data). This genomic island also contains phage-related genes, indicating the possibility of a phage-inducible island (32). In planta transfer of copper resistance genes encoded on this island has, however, not been successful in preliminary experiments. This is in contrast to the in planta transferable genomic island containing chromosomally encoded copper resistance genes in XVP26, an *Xv* strain isolated in Taiwan (12, 13). The structure of the genomic island in XVP26 is similar to that in *Xanthomonas arboricola*. Such chromosomally encoded copper resistance genes within a genomic island could be an adaptative strategy for a pathogen continuously exposed to copper, alleviating the fitness costs associated with maintaining large plasmids. However, failure to obtain successful in planta transfer of chromosomally encoded copper resistance genes from recent *Xp* lineages in the presence of copper raises questions about the potential to spread chromosomally encoded copper resistance between strains. With the findings that copper nanoformulations are effective in controlling copper-tolerant BLS xanthomonads (20, 73), risk assessment studies need to be conducted to understand how pathogen populations respond to the use of these new formulations and whether resistance might develop.

Role of asymptomatic pathogen reservoirs, volunteer plants, and alternate hosts. The contribution of an endemic pathogen population surviving in crop debris from the previous season, volunteer plants derived from self-set hybrids, and the presence of weeds or rotation crops as potential inoculum sources or in generating pathogen diversity cannot be ignored for BLS. Because more than one source of inoculum and more than one mechanism for delivering higher epiphytic populations can contribute to disease, understanding the relative quantitative contribution of each of these sources or dispersal mechanisms to the phyllosphere community during all stages of plant development is important. Although perennial weeds in tomato/pepper fields have been shown to be infected by the pathogen (6), their potential as an inoculum source is still questionable (51). Shotgun metagenomics sequencing of the weed phyllosphere indicated that weeds are reservoirs of considerable microbial diversity. There was significant overlap between saprophytic microbiota on weeds with that in the neighboring tomato/pepper phyllosphere. *Xp* was present with relatively low abundance (~1.5%) on asymptomatic weeds. This low abundance might indicate that weeds act as sinks rather than as a source of the pathogen. However, more sampling is necessary to reveal the effects of the environment on the relative abundance of BLS *Xanthomonas* on weeds, as high humidity conditions elevate epiphytic populations (83). How do volunteer plants/alternate hosts contribute to the exchange of adaptive traits in pathogens? For the conjugation-mediated transfer of genes/adaptive traits among lineages colonizing distinct ecological niches, cell-to-cell contact is required to share DNA directly. However, in some agricultural contexts (e.g., intercropping) and in the presence of extreme weather events, the physical proximity of plant species contaminated by different pathogens could facilitate contact and HGT (31).

Influence of Co-Occurring Phyllosphere Colonizers on Disease Dynamics

MAMPs: microbe-associated molecular patterns

NLRome: diverse set of NLRs accounting for the integrated domain diversity, presence/absence polymorphisms

Bacterial spot–infested tomato/pepper plants are often simultaneously infected by other bacteria, the symptoms of which are often indistinguishable from bacterial spot. Opportunistic or weaker pathogens such as *X. arboricola* and potentially novel species closely related to *Xanthomonas translucens* and *Xanthomonas sacchari* (M. Pena, J. Jones, R. Stall, N. Potnis, M-A. Jacques, unpublished data) have been simultaneously isolated from infected tomato/pepper transplants/fields (37, 126). As these pathogens are pectolytic, they can cause fruit lesions and leaf spot/chlorosis symptoms under high humidity conditions (78, 82). These opportunistic xanthomonads are important members of the BLS-associated phyllosphere community (83, 99); thus, the extent to which they influence the survival, virulence, and transmission of the BLS pathogen needs to be investigated. The variable presence of the type III secretion system and the fact that there are only a few effectors in these strains might explain their opportunistic nature; however, their capacity to act as reservoirs or hubs for the transfer of adaptive traits remains to be understood (21). *X. campestris* pv. *raphani*, primarily a crucifer pathogen, was recently shown to cause outbreaks of leaf spot and wilt on tomato (94). *Xp* was reported as the causal agent of pith necrosis, in which *Pseudomonas* spp. (*Pseudomonas mediterranea*, *Pseudomonas cichorii*, *Pseudomonas fluorescens*, *Pseudomonas putida*, *Pseudomonas marginalis*, and *Pseudomonas viridiflava*) were shown to mediate synergistic interactions with *Xp* (4). *Pseudomonas floridensis*, *P. viridiflava* (50), and *Pseudomonas corrugata* (49) cause outbreaks in tomato fields, at times with BLS xanthomonads. The incidence of these outbreaks along with *Xanthomonas* warrants research into how the mixed infections might influence overall disease outcomes. For example, *P. floridensis* strains isolated from outbreaks in Florida (121) contained only nine type III effectors, and the *R* gene *Pto* can offer resistance in tomato against *P. floridensis* (29), but how a mixed infection influences the disease outcome is not known. In Canada and the northern United States, *P. syringae* pv. *tomato* and *Xg* coexist. Mechanisms and consequences for this coexistence are yet to be studied. In artificial inoculation studies resulting in mixed infections, *P. syringae* pv. *tomato* outgrew *Xeu* regardless of the ratio at which they were mixed. Heat-killed cells of either pathogen were unable to offer cross-protection from infection by the other on susceptible tomato (108). The co-colonizing microbes, either pathogens, opportunists, or saprophytes, can affect disease outcomes through either direct interaction such as antagonism (110) or indirect interaction through niche construction by manipulation of plant defense responses, resulting in influence on virulence, pathogen multiplicity, disease aggressiveness, or transmission (68, 116, 131). They are also hypothesized to influence the adaptive potential of a pathogen population by fostering genetic exchanges that lead to the generation of diversity (26, 45). The extent to which these mixed infections contribute to BLS pathogen emergence, shifts in the lineages, and race shifts needs further attention.

AN INTEGRATED APPROACH CONSIDERING THE DISEASE PYRAMID FOR MANAGING THE DISEASE

Equipping ourselves with an understanding of the multifaceted interplay within the host–pathogen–microbiome–environment system can help us tailor disease management practices in agroecosystems (**Figure 1**). Resistance-based disease management continues to play a significant role in integrated pest management strategies. **Figure 3** outlines a general plan with multiple approaches that have been or can be harnessed to identify breeding targets by integrating knowledge of population genomics and the associated core effectors, fitness factors, and microbe-associated molecular patterns (MAMPs) of diverse BLS pathogens as well as synergistic partners and the NLRome. This includes (*a*) spatiotemporal shotgun metagenomics approaches or isolate genome sequencing for extensive isolate collections around the world to identify gene-to-genome-to-population level adaptive changes in the pathogen occurring in both seed production and fruit

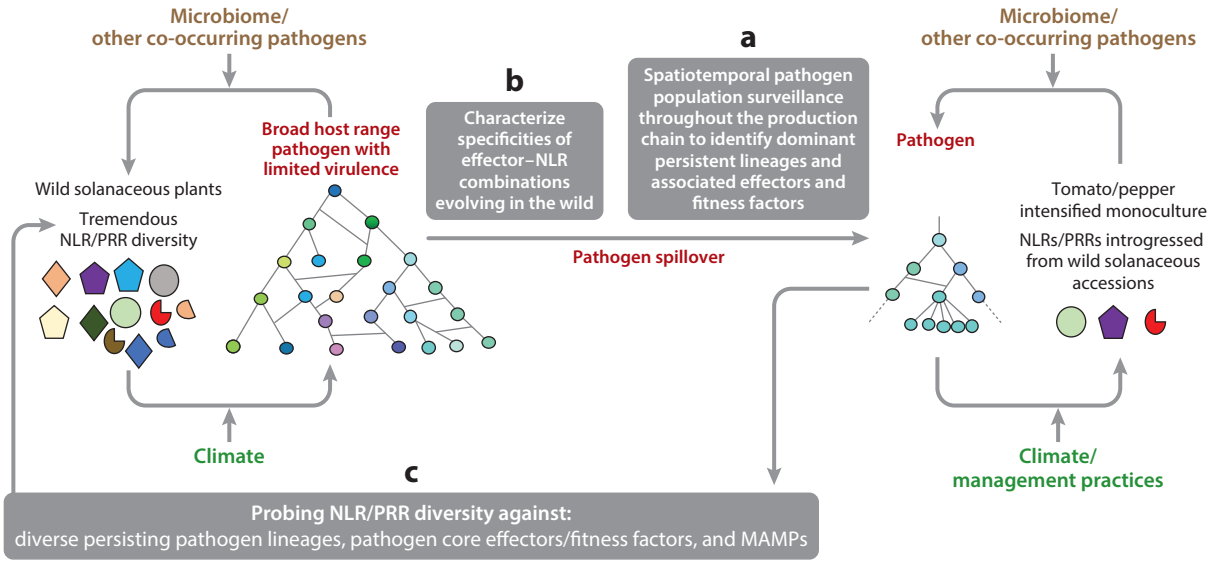

Figure 3

Pathogen population genomics as well as a characterization of diversity of NLRs/PRRs from natural and agricultural ecosystems can help plant pathologists harness the plant–pathogen coevolutionary arms race to achieve resistance-based management. This requires the following approaches. (*a*) Understanding altered host–pathogen interactions in response to resistance host genotypes as well as modern agricultural practices. This approach requires spatiotemporal surveillance of pathogen populations around the world to inform associations of persisting pathogen lineages as well as their associated effector combinations to a variety of disease risk factors in the modern agroecosystems. The components of the disease pyramid indicated in **Figure 1** determine the relative abundance and success of the pathogen lineages as a part of pathobiome. (*b*) Understanding the stabilized coevolutionary arms race involving broad host range pathogens (with limited virulence) and wild solanaceous varieties carrying a diverse NLRome to evaluate the range of specificities among effector/NLR combinations evolving in the wild to recognize a broad range of pathogens. We can harness already characterized NLRomes from wild tomato and peppers (62, 71, 107). (*c*) Probing the complex NLR network against diverse pathogen lineages carrying diverse sets of virulence factors or fitness factors (9). We could benefit from the great diversity of NLRs in wild solanaceous plants, where functionally redundant helper NLRs work with different sensor NLRs such as *Bs2*, *Sw5*, and *Prf* to confer immunity against multiple pathogens such as *Xanthomonas*, *Tomato spotted wilt virus*, and *Pseudomonas* (132). A similar approach has been taken for developing screens to identify PRRs against diverse alleles of MAMPs. These large screens spanning diverse NLRs or PRRs can be useful in developing resistance against a broad range of pathogens. Abbreviations: MAMPs, microbe-associated molecular patterns; NLRs, nucleotide-binding and leucine-rich repeat immune receptors; PRRs, pattern recognition receptors.

production areas; (*b*) a survey of wild solanaceous varieties for diversity in pathogen populations to understand effector combinations present in diverse pathogens to which NLRs have evolved; and (*c*) the screening of wild solanaceous varieties or other plant families [for pattern recognition receptors (PRRs)] to identify NLRs/PRRs that recognize core effectors or the effectorome (9), fitness factors/MAMPs from the *Xanthomonas* (15, 100, 133), and co-occurring pathogens (that appear to influence the overall disease outcome). The **Supplemental Material** includes currently available resistance loci in tomato/pepper and corresponding core effectors/MAMPs that have been considered for resistance-based management strategies along with other putative candidates.

Resistance-based management is only effective if other risk factors responsible for outbreaks are also carefully considered as a part of a management strategy. Seedborne diseases require tracing outbreaks and collecting associated metadata followed by network analysis to inform control points before key genotypes are introduced and spread across the fields (34, 64). The research field is poised to evaluate other factors such as agronomic chemical applications, climate,

Supplemental Material >

NLRs: nucleotide-binding and leucine-rich repeat immune receptors

PRRs: pattern recognition receptors

the microbiome, and other co-occurring pathogens on disease outbreak potential as well as the adaptative potential of the pathogen (**Figure 1**). For example, the addition of fertilizer was shown to abolish phyllosphere microbiome-mediated host tolerance against *P. syringae* (14). Application of systemic acquired resistance–inducing compounds such as acibenzolar-*S*-methyl (typically used only on susceptible cultivars) to resistant cultivars delayed race shifts in pathogens (101). Thus, identifying the contribution of each of these factors to the risk of BLS outbreaks and their individual or combinatorial effects on pathogen evolution and overall host susceptibility to pathogens is a priority in optimizing sustainable disease management strategies.

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