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Tolerance of Plants to Pathogens: A Unifying View

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Abstract

Increasing evidence indicates that tolerance is a host defense strategy against pathogens as widespread and successful as resistance. Since the concept of tolerance was proposed more than a century ago, it has been in continuous evolution. In parallel, our understanding of its mechanistic bases and its consequences for host and pathogen interactions, ecology, and evolution has grown. This review aims at summarizing the conceptual changes in the meaning of tolerance inside and outside the field of phytopathology, emphasizing difficulties in demonstrating and quantifying this trait. We also discuss evidence of tolerance and current knowledge on its genetic regulation, mechanisms, and role in host–pathogen coevolution, highlighting common patterns across hosts and pathogens. We hope that this comprehensive review attracts more plant pathologists to the study of this key plant defense response.

INTRODUCTION

Understanding how plants defend themselves against pathogens is a central and long-standing goal in phytopathology. It is currently well established that the two main defenses of plants against pathogens are resistance, i.e., the host's ability to limit pathogen multiplication (22), and tolerance, i.e., the host's ability to reduce the negative effects of infection (22, 66). These represent two fundamentally different strategies to cope with pathogens: Resistance reduces the multiplication rate of the pathogen in the infected plant, whereas tolerance does not. These two defenses may lead to different outcomes of plant–pathogen interactions. It was proposed that resistance affects epidemic dynamics, and because resistance reduces the pathogen's fitness, it imposes a selection pressure on the pathogen that may eventually lead to the resistance breaking down (39, 141). Tolerance would not exert such a selection pressure and thus would be a more stable defense strategy (16, 140, 145), which is at the root of the interest in this host trait.

At odds with the extensive efforts devoted to understanding resistance, tolerance has been comparatively neglected, as demonstrated by the fact that the *Annual Review of Phytopathology* has not covered the subject since John F. Schafer's seminal paper published in 1971 (122). Plant pathologists seem to have been uncomfortable with tolerance because of conceptual and practical difficulties associated with researching it and its application in understanding pathosystems. One source of conceptual confusion is the indiscriminate application of the term tolerance to designate either endurance to disease or pathogen infection or partial levels of resistance between immunity and full susceptibility, two phenomena that are not always easy to differentiate. A major aim of Schafer (122) was to avoid this confusion and limit the use of the term tolerance to enduring infection/disease. This is now the commonly accepted meaning in pathology at large as well as the (broad) meaning used in this review. We should underscore, however, that the failure to distinguish between tolerance and partial resistance has persisted and occurs even in recent reviews on plant tolerance (90). Conceptual fluxes between plant and animal pathology in the past few decades and an increasing appreciation of the ecological and evolutionary consequences of host defenses have resulted in new conceptual formulations. This has prompted a renewed attention to tolerance.

In this review, we examine the different meanings and formulations of the concept of tolerance in plant pathology and in pathology at large, discuss difficulties in demonstrating and quantifying tolerance, and summarize evidence of tolerance and current knowledge about its genetic regulation, mechanisms, and role in host–pathogen coevolution. We are confident that this review will attract new plant pathologists to the study of tolerance.

TOLERANCE: AN EVOLVING CONCEPT

Tolerance is an old concept in phytopathology. The concept of tolerance in phytopathology was originally proposed in 1894 by Cobb (23, p. 340), who, while studying rust-enduring wheat varieties, found varieties that "though liable to rust, (are) able, notwithstanding the attack of the rust, to mature a fair crop of grain under ordinary circumstances." Imprecise as this definition may seem today, it includes the essential concepts of endurance and pathogen attack, which are both central to tolerance. During the first half of the twentieth century, research on fungal diseases of small grain cereals provided new evidence of the relevance of tolerance. For example, Flor et al. (33) reported on wheat varieties with a twofold difference in bunt increase but similar grain yield. Similarly, Peturson et al. (100) reported that two levels of leaf rust produced similar grain yield losses in three wheat varieties. These early studies brought attention to tolerance as a relevant component of plant–pathogen interactions and suggested that tolerance could be a form of crop

protection against pathogens. A landmark study by Caldwell et al. (16, p. 714) on the effects of crown rust on oats defined tolerance as the quality "enabling a susceptible plant to endure severe attack by a rust fungus without sustaining severe losses in yield or quality." Other early definitions included the effects of tolerance on disease severity in addition to, or rather than, yield or quality loss. Thus, the American Phytopathological Society in its 1940 Report on Technical Words, defined tolerance as "the ability of the affected organism to endure the operation of a pathogenic factor or invasion by a pathogenic organism or virus with little or no reaction, as shown by more or less complete absence of symptom expression and damage" (in 14, p. 91).

Further conceptualization was attempted by Schafer (122, p. 239), who defined tolerance as "that capacity of a cultivar resulting in less yield or quality loss relative to disease severity or pathogen development when compared with other cultivars or crops." This definition can be taken as the origin of our current understanding of tolerance, as it underscores the quantitative and relative nature of tolerance and the fact that it is genetically determined. It also conveys the idea, further developed by Schafer (122), that tolerance has to be measured in conditions in which the cultivars to be compared sustain similar levels of pathogen load throughout the infection period, which allows differentiation between tolerance and partial resistance. However, Schafer recognized the difficulty of establishing such experimental conditions for quantifying tolerance and proposed relaxing them to the comparison of pathogen loads at a fixed time point during the infection period.

All these earlier definitions were in the context of crop protection, restricting the effect of pathogen infection or disease on plant yield or quality. These definitions maintained ambiguity regarding tolerance to disease or tolerance to pathogen attack. Clarke (22, p. 168) made the distinction between tolerance of (or to) the parasite, tolerance of (or to) disease, and overall tolerance, defining overall tolerance as "the ability of a plant to endure the effects of levels of parasitic infection and disease which, if they occurred at equivalent levels in other plants of the same or similar species, would cause greater impairment of growth or yield." This definition has remained valid and in use until now (e.g., 15). However, as with the definitions above, it is intrinsically limited by the difficulty of defining and quantifying disease (14) using the typical approaches of rating symptom expression or the effects of disease on plant production or growth.

Interest in the effects of pathogens on plants in nonagricultural systems beginning in the late 1970s required reformulating tolerance in terms other than losses in yield or quality. This was coincidental with the perception of the need for a nonanthropocentric concept of plant disease, considered as a process that by impairing plant functions negatively affects the biological system itself rather than specific parameters such as growth or yield (7). Bos & Parlevliet (14, p. 92) defined tolerance as the "ability of a host to limit the harmful effects of a parasite or phytophagous organism or of an abiotic factor," where the harm can be interpreted as, primarily, to the host itself or, secondarily, to the host's user (the grower). An equally simple and precise definition of tolerance is that it is a host trait that reduces the detrimental effects of parasite infection, as opposed to resistance, which reduces the success of an infection process or increases the rate of parasite clearance (52, 106).

As evidence accumulated during the second half of the twentieth century that tolerance was a plant defense strategy as widespread as resistance (86), the study of tolerance expanded beyond phytopathology. Tolerance was recognized as an important component of animal defenses against parasites and as relevant to human health (63, 104, 107, 145), which then required that tolerance be defined for hosts other than plants. The definitions by Bos & Parlevliet (14), Restif & Koella (106), and Jeger and coworkers (52) underscored the negative effects of infection on the host itself. The degree of the negative effect is termed virulence (14, 26), or aggressiveness (sensu van der Plank)

(141), by plant pathologists. Virulence can be related to many host traits (e.g., symptom severity, biomass production) but is often defined as the reduction of host fitness caused by pathogens (37, 105). This definition originated within the field of evolutionary biology and can be applied to any living system. It has the advantage of eliminating any anthropological perspective and connects the effects of disease in individuals with host population dynamics and evolution. According to this concept of virulence, tolerance has been defined as "the ability of hosts to limit the damage caused by a given parasite burden, which is essentially the ability to minimize per-parasite virulence" (66, p. 2). Similarly, Råberg (102, p. 2) defined tolerance as "the ability of a host to limit the health or fitness effect of a given infection intensity." These definitions eliminate the distinction between tolerance to parasites and tolerance to disease and currently are broadly accepted.

This summary of more than a century of definitions of tolerance shows that, although they may differ in precision or focus, all underline two main features: (*a*) the reduction of the negative effects of pathogen infection on the host (*b*) without affecting pathogen multiplication. However, none of the definitions eliminates the difficulty of quantifying disease and/or its effects (39). Measuring host fitness is not trivial (37, 58, 117) and may be impractical for many crops or long-lived plants.

QUANTIFYING TOLERANCE AND ITS RELATIONSHIP WITH PATHOGEN INFECTION LEVELS

The various definitions of tolerance emphasize different host and pathogen traits as relevant to understand this host defense. Such heterogeneity results in different parameters being measured and in different procedures of quantifying tolerance. Consequently, studies may be difficult to compare and sometimes lead to inconsistencies (66, 86). Also, demonstrating tolerance requires quantifying pathogen infection/multiplication and showing that infection endurance is not due to partial resistance. We develop these two topics in this section.

Traits for Quantifying Tolerance

An initial difficulty for every measure of tolerance is defining the trait on which endurance to pathogen attack is evaluated. Crop studies put the emphasis on yield reduction, e.g., amount of grain for cereals (36, 62, 79), fruit for tomato or zucchini (13, 27), or biomass for sugarcane (42, 121). As pathogen infection may also reduce the quality of the crop product, quality is also considered when evaluating tolerance. Thus, bushel weight of grain was measured to analyze wheat tolerance to leaf rust (16, 110).

Emphasis on the effects of disease on the host itself rather than on host production leads to an evaluation of tolerance according to how virulence is defined. When virulence is understood as a reduction of host fitness, its quantification is usually approximated through one fitness component. Most models of virulence evolution quantify virulence in terms of increased host mortality or reduced survival (1, 2, 105). Mortality tolerance is thus the host trait that reduces the effects of pathogen infection on host survival. Many studies of animal tolerance to pathogens quantify mortality tolerance (8, 63, 103, 111), as this trait is easy to measure and is highly relevant in the analysis of infection effects on livestock and humans (8, 63, 107, 139). Mortality tolerance has been less often analyzed in plants, with some exceptions (46, 77, 92, 94, 96, 144). Interestingly, the mortality of infected plants may correlate with other parameters that are easier to measure, such as reductions in leaf area or increases in symptom severity, as shown for *Brassica rapa* and *Arabidopsis thaliana* plants infected by Cauliflower mosaic virus (CaMV) (30).

Virulence can also be measured by its impact on other fitness components, such as fecundity, which leads to estimates of fecundity tolerance (86). In plants, fecundity can be estimated by the number of viable seeds produced per plant or by correlates such as number of flowers or fruits.

Plant fecundity tolerance has been analyzed more often than mortality tolerance (e.g., 19, 49, 88, 92, 95, 120, 130). It is important to stress that mortality and fecundity tolerance need not be correlated and may vary differently with pathogen load or with the rate of pathogen multiplication or may vary similarly as a function of pathogen load or the rate of pathogen multiplication. Theory and model simulations show that fecundity tolerance is a monotonously growing (to saturation) function of mortality tolerance or may have a relative maximum, depending on pathogen virulence, which is measured as mortality (11).

Although both mortality and fecundity are easy to measure in short-lived annual plants, this is not the case for long-lived annuals or perennials. Thus, tolerance is estimated through proxies of mortality or fecundity. Fecundity and biomass are often correlated (e.g., 12), and biomass or the processes determining final biomass, such as growth rate or photosynthetic activity, have been used to estimate tolerance (123, 126, 132). However, biomass may not always be positively correlated with fecundity tolerance. Biomass and fecundity tolerance may not be correlated if fecundity tolerance is attained by reallocation of resources from growth to reproduction, as found in genotypes of *A. thaliana* tolerant to Cucumber mosaic virus (CMV) infection (83, 84). Last, fecundity and mortality tolerance can be quantified on the basis of disease severity. Measures of disease severity based on symptom development are common and more or less precise and reproducible (50). Thus, the relative leaf area that is affected by the action of pathogens that cause local infections can be quantified precisely, objectively, and reproducibly (55). More problematic are qualitative symptom severity ratings for diseases caused by systemic pathogens such as viruses (17). However, symptom severity ratings may still prove to be useful for the estimation of tolerance (30).

Thus, among the different major fitness components, such as fecundity or survival, and their different correlates, researchers must carefully choose the procedure to estimate tolerance according to the specific pathosystem, the aims of the study, and the hypotheses to be tested. Otherwise, analyses may lead to ambiguous conclusions about tolerance of plants to pathogens.

Equivalent Levels of Pathogen Infection: Differentiating Tolerance from Resistance

Since Cobb's definition in 1894, it has been stressed that more tolerant varieties better endure the effects of infection than do less tolerant ones at the same level of pathogen attack. The emphasis on equivalent level of pathogen attack is necessary to differentiate bona fide tolerance from partial resistance. Pathogen attack has been quantified most often as the pathogen load sustained by the host (22, 86, 122), which depends on the rate of within-host pathogen multiplication, i.e., on the resistance/susceptibility of the host, all else being equal.

Disease severity, i.e., virulence, is assumed in most models of virulence evolution to be positively correlated with within-host pathogen multiplication (1, 2, 37, 105). Tolerance breaks the relationship between pathogen load and virulence (73). A major question is whether the correlation between pathogen multiplication and virulence holds for all host–pathogen interactions. Evidence supporting this hypothesis exists for all classes of plant pathogens (reviewed in 117). For example, pathogen multiplication was positively correlated with virulence in wheat and *Puccinia triticina* or *Mycosphaerella graminicola* (109, 149), potato and *Phytophthora infestans* (74), *A. thaliana* and *Pseudomonas syringae* (61), and rice and Rice yellow mottle virus (32). However, the relationship between virulence and pathogen multiplication is far from universal (e.g., 31, 55, 83, 116, 134) and seems to be less common for viruses whose pathogenesis largely depends on deregulation of host gene expression (88). Finally, virulence can be a function of the phenological stage at infection and the variation in pathogen load over time, with high multiplication rates occurring early in the infection period having different impacts on virulence than those occurring late in the infection period (12).

The difficulty of estimating tolerance because of the complexity of the relationship between virulence and pathogen load is implicit in Schafer's (122) recommendation that true tolerance should be identified by comparing reactions to a similar pathogen load throughout the infection period. However, Schafer was aware that this could be impractical and that analyses could be relaxed to consider comparisons under similar pathogen load at the same host phenological stage. This forms the basis of the concepts of range tolerance and point tolerance.

Range and Point Tolerance

As the relationship between virulence and pathogen multiplication is ambiguous and, when it exists, often nonlinear, the comparison of tolerance levels between host varieties or genotypes is best studied following the formal analysis of a reaction norm across environments (125), here corresponding to different pathogen loads. Tolerance, considered as a reaction norm (101, 130), is represented by the slope of a regression of host fitness against pathogen load: the steeper the slope, the lower the tolerance (129). This metric is referred to as range tolerance (66). Measuring tolerance as a norm of reaction has the advantage of allowing for linear and nonlinear relationships between host fitness and pathogen load and, additionally, provides a method for estimating potential costs of tolerance (101, 130). Interestingly, because tolerance is defined as the slope of the host fitness to pathogen load regression, range tolerance is expressed per unit of pathogen load (66). A similar measure of tolerance to pathogens was proposed by Frantzen (38) using an epidemiological argument rather than a reaction norm. Range tolerance was first used to analyze tolerance of plants to herbivores (130) and has also been applied to pathogens (66, 86, 102). However, pathogen load is more difficult to control in experiments than herbivore pressure, as the relationship between pathogen load at any time during the infection period and inoculum dose is complex. Thus, most experiments aiming at estimating range tolerance to pathogens use a single inoculum dose, and pathogen load then varies according to a combination of intrinsic parasite replication rate and host defenses, i.e., load is an uncontrolled outcome of the experiment. The resulting differences in pathogen load provide the variation against which fitness regresses (63). Indeed, it has been proposed that comparison of these regressions is the most suitable approach for the analysis of tolerance (56, 57). Range tolerance of plants to pathogens has been analyzed for different systems (e.g., 19, 49, 60, 130, 148). In many studies in crops, the measure of tolerance is derived from the slope of the relationship between yield and amount of disease [area under the disease progress curve (AUDPC)] (12). This measure is used mostly for fungi causing local leaf infections, and the AUDPC is estimated from the fraction of damaged leaf area (e.g., 79, 89), in which case the damaged leaf area is equivalent to the pathogen load for a given pair of host and pathogen genotypes and the AUDPC estimate is equivalent to range tolerance.

Although there is a general agreement that range tolerance is optimal for quantifying tolerance (86), it also has limitations. The most obvious one is that the assumed positive correlation between virulence and pathogen load, discussed above, may not hold. In these cases, range tolerance may not be an appropriate measure. In addition, determining the reaction norm of the relevant trait for tolerance in a sufficiently large range of pathogen loads is cumbersome and may be impractical when a large number of plant genotypes are to be compared, e.g., in studies on the genetic variation of tolerance. An alternative is to estimate point tolerance (66). Point tolerance is studied as a means of comparing the host fitness of different genotypes under the same pathogen load. As with range tolerance, point tolerance captures the essential feature of reducing per-parasite virulence (66). A main limitation of point tolerance compared to range tolerance is that it ignores the fact that hosts may differ in their ability to cope with the effect of infection depending on pathogen load (66, 102). For example, a given plant genotype may suffer little from infection when pathogen load is low but

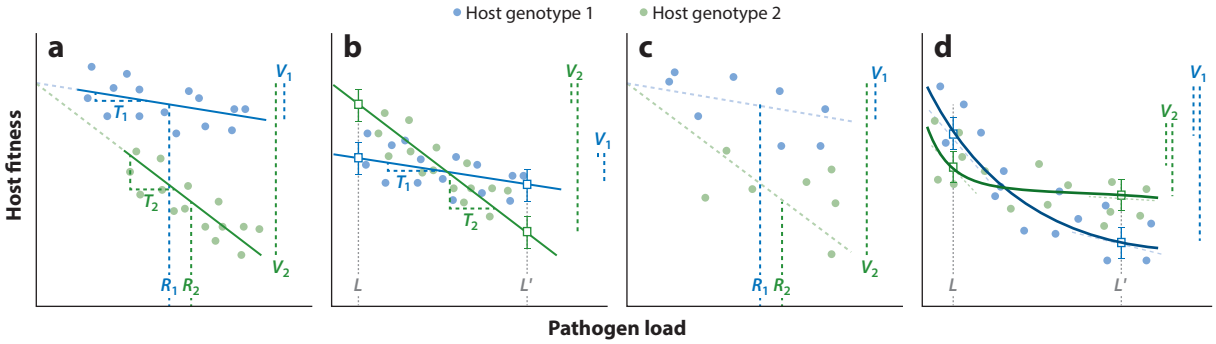

Figure 1

Relationship between different measures of tolerance. (*a*) Host genotypes 1 (*blue*) and 2 (*green*) have the same fitness when uninfected. Resistance (*R*) and range tolerance (*T*) are higher for genotype 1 than for genotype 2. The ranking of the two genotypes is the same for range tolerance, as well as for point tolerance and the effect of infection on host fitness (*V*) normalized to the uninfected host, across pathogen loads. (*b*) Host genotype 1 (*blue*) has lower fitness than genotype 2 (*green*) when uninfected, but range tolerance *T* is higher for genotype 1 than for genotype 2. Point tolerance (*open squares*) is the same as range tolerance at pathogen load *L′* but not at *L*. The normalized effect of infection of *V* always agrees with *T*. (*c*) Host fitness *V* does not vary significantly with pathogen load, as indicated by the dashed lines. Only point tolerance and the normalized effect of infection on *V* can be estimated. (*d*) The relationship of host fitness *V* to pathogen load is nonlinear. The ranking of the genotypes for tolerance depends on pathogen load no matter the measure, but the ranking is the same for *T* and the normalized effect of infection on *V* but different for point tolerance. In panels *a* and *c*, resistance (*R*) for the mean values of pathogen load is indicated.

have a great reduction in fitness at a high pathogen load, whereas infection may reduce the fitness of another genotype at intermediate levels for a large range of pathogen loads: At low pathogen loads, the first host genotype can be more tolerant than the second host genotype, but at high pathogen loads, the second host genotype can be more tolerant than the first. Hence, conclusions derived from point tolerance may vary depending on the (same) pathogen load in the compared genotypes. Note, however, that the Little et al. (66) argument assumes that comparisons are among infected genotypes. If tolerance is estimated from the fitness of the infected plant normalized to that of noninfected controls, this problem disappears provided that the relationship between virulence and pathogen load follows the same function (e.g., linear, negative exponential, etc.) for all genotypes. Comparison of plant fitness or its correlates with uninfected controls is the measure of tolerance in most studies (e.g., 18, 61, 84, 85, 95). A comparison of the different measures of tolerance is shown in **Figure 1**.

Despite the interesting debate on the optimal way of measuring tolerance, analyses simultaneously comparing conclusions derived from different tolerance measures in the same pathosystem have not been reported. This analysis has been done for *A. thaliana* genotypes infected by two viruses, CMV and Turnip mosaic virus (TuMV). Analyses indicate that regardless of whether tolerance is quantified as the slope of plant fitness to virus load regression or as the fitness of the infected plant normalized to that of uninfected controls; conclusions regarding trade-offs between tolerance to different viruses were consistent (77) (**Figure 2**).

EVIDENCE OF TOLERANCE AND MECHANISTIC BASES

Despite concerns about the possibility of demonstrating tolerance (22, 39, 122), a large body of evidence has accumulated showing the relevance of tolerance in plant–pathogen interactions. Here, we summarize this evidence and the current knowledge of the genetic and mechanistic bases of tolerance and how environmental heterogeneity affects its expression.

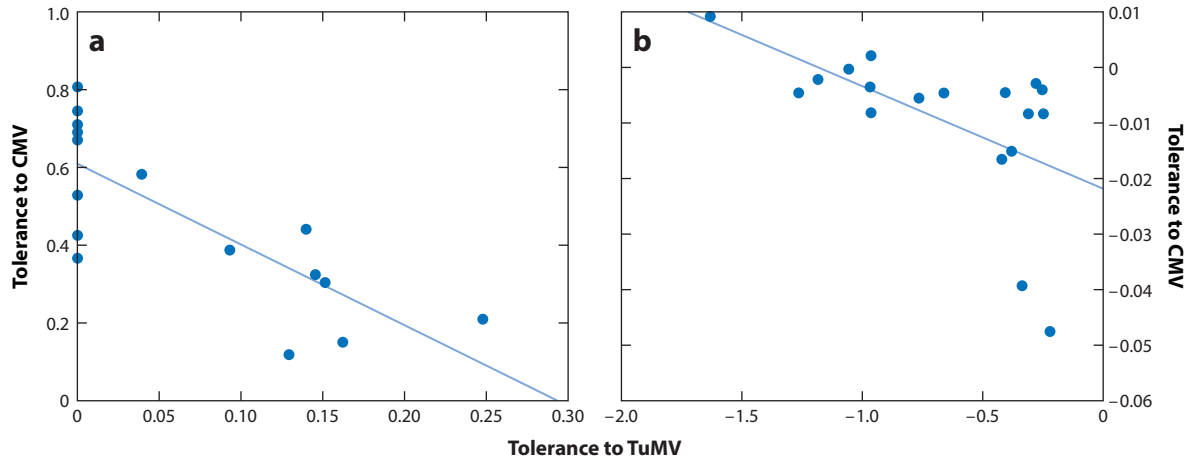

Figure 2

Comparison of different measures of tolerance. Relationship between the tolerance of 18 *Arabidopsis thaliana* genotypes to Cucumber mosaic virus (CMV) and Turnip mosaic virus (TuMV) when (*a*) tolerance was quantified as the effect of infection on per-plant seed production as compared with the corresponding uninfected control or when (*b*) tolerance is quantified as the slope of the regression of plant fecundity to virus load. Data from Reference 77.

Evidence of Tolerance of Plants to Pathogens

Until the 1950s, evidence of tolerance derived from studies with fungal pathogens (22, 86, 122). Many early analyses in crops focused on tolerance to rusts (*Puccinia* spp.) in cereals, reporting similar grain yields at different disease intensities (e.g., 16, 33, 100). Although some of these observations were later shown to be due to resistance responses (131), genetic variation for tolerance to cereal rust in several cultivars has been demonstrated more recently (62, 110, 135). Cereal and soybean tolerance to *Septoria* spp. and *Phakopsora pachyrhizi*, respectively, have also been widely documented (20, 36, 51, 59, 71, 89, 149). The study of tolerance to other plant pathogens followed. Tolerance to viruses has been studied in a few crops, e.g., in tomato to Tomato yellow leaf curl virus (TYLCV) (64, 115), in cereals to Barley yellow dwarf virus (BYDV) (35, 53, 108), in cowpea to Blackeye cowpea mosaic virus (3), or in zucchini to Zucchini yellow mosaic virus (ZYMV) (27). Tolerance to nematodes was also recognized to be widespread (136) and, particularly for root-knot and cyst nematodes (species of *Meloidogyne*, *Globodera*, and *Heterodera*), has been repeatedly reported in many crops, including potato, soybean, cereals, chickpea, okra, and cotton (e.g., 4, 136, 137, 148).

Although one initial thrust for studying tolerance was the expectation of an effective disease control strategy when breeding resistance is difficult or protection by fungicides or resistance genes is overcome (20, 71, 78), tolerance in wild plants has also been studied, with studies dating back to the 1970s. Again, the earlier literature is biased toward plant–fungal interactions and included systems as varied as *Ipomea purpurea–Colletotrichum dematium*, *Senecio vulgaris–Erysiphe fischeri*, and *S. vulgaris–Puccinia lagenophorae* (9, 91, 130). Particularly noteworthy is the series of studies on the tolerance of *S. vulgaris* to *P. lagenophorae* and its physiological components and environmental modulators (54, 94, 95, 97) (see the section titled Modulation of Tolerance by the Environment). More recently, tolerance to rust fungi has also been studied within a community of perennial bushes (114). Tolerance of *A. thaliana* to *Hyaloperonospora arabidopsidis* (118, 120) and

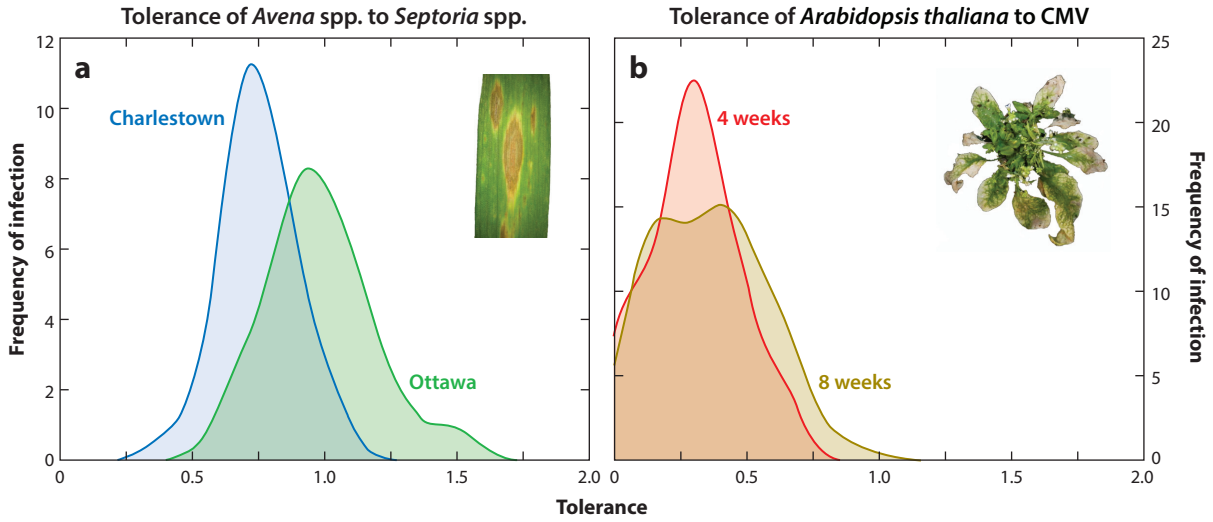

Figure 3

Tolerance as a quantitative trait. (*a*) Frequency distribution of tolerance values in 48 varieties of *Avena* spp. to *Septoria* spp. in two Canadian locations: Charlestown (*blue*) and Ottawa (*green*). (*b*) Frequency distribution of tolerance values in 80 genotypes of *Arabidopsis thaliana* to Cucumber mosaic virus (CMV) in plants vernalized for four (*red*) or eight (*olive*) weeks. In both studies, tolerance was measured as an effect of infection on per-plant seed production as compared with the corresponding uninfected control. Data in panel *a* are from Reference 21 and data in panel *b* are from Reference 75.

Solanum dulcamara to *P. infestans* (67) has been also reported. The role of tolerance in wild plant–virus interactions has focused on two model species in evolutionary ecology, and point and range tolerance of *Mimulus guttatus* (18, 19) and *A. thaliana* (47, 75, 77, 84) to CMV have been documented. *A. thaliana* genetic variation for tolerance to *P. syringae* and *Pseudomonas viridiflava* has also been demonstrated (43, 44, 61). Finally, tolerance to parasitic plants has also been shown, e.g., in the cactus *Echinopsis chiloensis* to the mistletoe *Tristerix aphyllus* and in *Urtica dioica* to *Cuscuta europaea* (60, 69). In *U. dioica*, genetic variation for tolerance depends on the plant sex.

In conclusion, there is a large body of evidence showing that tolerance to pathogens is a plant defense as effective and widespread as resistance and may play an important role in plant disease control, the dynamics of pathogen infection, and plant–pathogen coevolution.

The Genetics of Tolerance

Studies in crops and wild plants have provided ample evidence (22, 86, 122) that tolerance is a quantitative trait with a relevant genetic component, as shown in its variation among genotypes (**Figure 3**).

The genetic determination of tolerance has been analyzed in relatively few plant–fungal systems. For example, Han et al. (45) identified eight quantitative trait loci (QTLs) associated with soybean tolerance to *Phytophthora sojae*, and Ogrodowics et al. (81) detected 70 QTLs related to *Fusarium*-induced symptoms in barley. By contrast, considerable efforts have been made to determine the genetic bases of tolerance to viruses. A common trend is that a few QTLs of major effect control tolerance to viruses. Tolerance to TYLCV in tomato has been linked to 1–5 genes (65, 143). Similarly, tolerance to BYDV in barley and oats was associated with the effect of one to six QTLs (35, 54, 108, 124, 151), as opposed to tolerance in wheat to BYDV being explained by

22 QTLs of minor effect (5). Major QTLs have also been identified as determining the tolerance of *A. thaliana* to CMV (82) and of rice and wheat to root-knot and cyst nematodes, respectively (40, 146). However, tolerance of *A. thaliana* to *Xanthomonas campestris* is determined by a single dominant gene *RXC1* (138).

Mechanisms of Tolerance

Plastic modification of life-history traits may be an adaptive mechanism to selection pressures such as parasitism or disease (133). Because parasites may affect host resource allocation and developmental time schedules, it has been proposed that life-history modifications may be host responses to compensate for the negative effects of parasitism, i.e., to attain tolerance (34, 41, 48, 99). Abundant studies with plants support this hypothesis. In fungi infecting leaves locally, virulence may be related to the effects of infection on the duration and extension of the green leaf area (12, 89). Accordingly, tolerance has been associated with compensatory increases of photosynthetic activity in noninfected tissues compared with infected ones (80). For example, tolerance of *S. vulgaris* to *Coleosporium tussilaginis* and *P. lagenophorae* was mediated by higher CO_2 fixation at the leaf and whole plant scales, and/or reduced photorespiration (49, 91). Compensatory increases of photosynthetic activity in noninfected leaf areas were also shown to be associated with tolerance in *Puccinia coronata*–infected oats (126) or wheat cultivars tolerant to *Septoria tritici* (152). Compensatory photosynthesis can result in reallocation of photosynthates to different leaf areas, leaves, or plant parts. Resource reallocation between different plant organs, e.g., from roots to shoots and vice versa, has been reported in response to foliar and root pathogens, respectively (6, 92, 112). Mobilization of carbohydrates from the stem to filling grains may also be a mechanism of tolerance to foliar fungi in wheat (12, 25, 36). Resource reallocation from growth to reproduction is not limited to tolerance to fungi. It has been linked to tolerance of *U. dioica* to *C. europaea* (60). *A. thaliana* tolerance to CMV and TuMV is also associated with resource reallocation from growth to reproduction; thus, upon infection, rosette growth is more severely inhibited in tolerant genotypes than in nontolerant ones, but the effect of infection in the development of inflorescences and in seed production is much reduced (47, 75, 77, 84). However, resource reallocation is a virus-specific response of tolerant genotypes, not a general response of *A. thaliana* to the stress of virus infection, as a virus-specific response of tolerant genotypes (128).

Changes in life-history traits associated with tolerance also include rescheduling of the temporal pattern of development. Thus, tolerance of *A. thaliana* to *H. arabidopsidis*, *P. viridiflava*, or highly virulent isolates of TuMV was associated with accelerated plant bolting (43, 77, 120), whereas tolerance to the less virulent CMV and TuMV isolates was associated with delayed flowering (47, 77, 84, 128). Also, the *A. thaliana* accession C24, which is tolerant to *Verticillium dahliae*, delayed flowering upon infection; this did not occur in accession Col, which is not tolerant to *V. dahliae* (142). These results suggest that modulation of flowering time in tolerant genotypes of *A. thaliana* depends on the virulence of the infecting pathogen. Interestingly, genotypes tolerant to CMV were not tolerant to TuMV and vice versa, indicating trade-offs between tolerance to different viruses (77).

The mechanisms behind these life-history trait responses have been analyzed in some systems. Potato (*Solanum tuberosum*) tolerance to Potato virus Y (PVY) is linked to increased photosynthesis due to early activation upon infection of the photosynthetic apparatus and RuBisCO upregulation (132). Also, salicylic and jasmonic acids may be involved in tomato tolerance to TYLCV (65). Tolerance of *A. thaliana* to *P. syringae* has also been associated with increased biosynthesis of salicylic acid (150). Lastly, tolerance of *A. thaliana* to CMV requires functional alleles of flowering repressor genes, whose expression might be regulated upon infection (127).

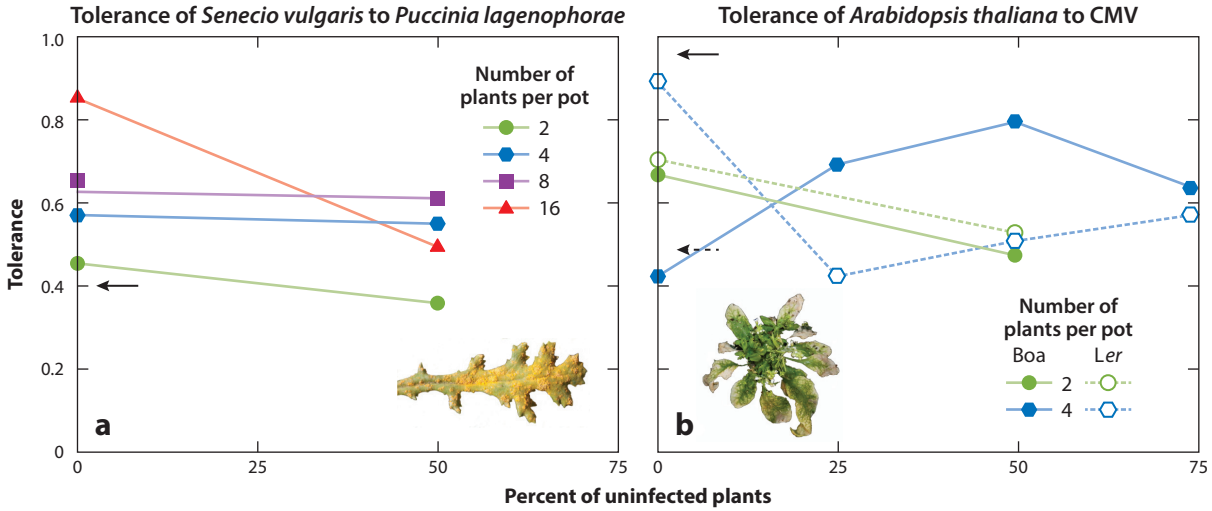

Figure 4

Effect of plant density on fecundity tolerance. (*a*) Tolerance of *Senecio vulgaris* to *Puccinia lagenophorae* at densities of 2, 4, 8, and 16 plants per pot and different proportions of uninfected plants. Data from Reference 92. (*b*) Tolerance of *Arabidopsis thaliana* accessions L*er* (*dashed lines*) and Boa (*continuous line*) to Cucumber mosaic virus at densities of 2 and 4 plants per pot and different proportions of uninfected plants. Data from Reference 85. Black arrows indicate tolerance at one plant per pot (in panel *b*, the dashed arrow indicates L*er* and the solid arrow indicates Boa).

In summary, compensatory changes in life-history traits seem to be a common process for attaining tolerance to different pathogens. However, there is only fragmentary information on the underlying mechanisms, which does not provide a general picture of the mechanisms of tolerance.

Modulation of Tolerance by the Environment

Phenotypic plasticity is relevant in host–pathogen determined traits (68, 70). Thus, environmental heterogeneity, resulting in the variation of factors such as intra- or interspecies competition, temperature, light intensity, and nutrient or soil water availability, among others, could modulate tolerance. Experimental analyses of the effects of environmental heterogeneity on tolerance mostly quantified fecundity tolerance, unless indicated otherwise.

The effects of intraspecific and interspecific competition on tolerance are complex and have been best analyzed in the system *S. vulgaris–P. lagenophorae*. For example, Paul & Ayres (92) reported that competition of rusted plants with noninfected ones at different plant densities resulted in a bimodal distribution of tolerance, with some plants suffering more and some less from infection (**Figure 4*a***). In this system, water stress decreased tolerance and the competitive ability of rusted plants (97), and nutrient availability modulated tolerance, with plants being more tolerant to rust infection at low nutrient levels (93). When *S. vulgaris* plants were grown in competition with *Capsella bursa-pastoris* plants, tolerance of *S. vulgaris* to *P. lagenophorae* depended on nutrient availability and the proportion of infected plants (98). Also, Pagán et al. (85) showed that *A. thaliana* plant density and the proportion of infected plants modulated tolerance to CMV for three plant genotypes, with tolerance depending on the plant density–host genotype interaction (**Figure 4*b***).

The effect of the abiotic environment on tolerance has also been analyzed. For example, the overwintering mortality of *S. vulgaris* was increased by rusting, but the rusted survivors produced more progeny in the spring that the nonrusted ones (94). This overcompensation was not

observed in nonoverwintering summer cohorts (96). In the *A. thaliana*–CMV system, winter severity simulated by different vernalization periods did not affect tolerance (75) (**Figure 3*b***). Hily et al. (47) provided evidence that increased light intensity boosted *A. thaliana* tolerance to CMV. Temperature modulated the effects of light on tolerance so that at high light intensity and moderate temperature overcompensation occurred in the tolerant genotypes. Expanding this work, Montes & Pagán (76) showed that *A. thaliana* tolerance to TuMV was also positively associated with light intensity. Finally, drought conditions have been shown to affect tolerance; for example, water stress decreases *S. vulgaris* tolerance to *P. lagenophorae* (97), whereas mortality tolerance to infection by several viruses has been shown to be higher under drought conditions (147).

The work summarized here indicates that tolerance responses vary with the environment and that these changes depend on the host genotype, thus showing the genetic and phenotypic plasticity components of tolerance. However, current analyses focus on one or, at most, two environmental factors, and multifactorial analyses are lacking.

TOLERANCE AND PLANT–PATHOGEN COEVOLUTION

Tolerance improves plant survival and fecundity without restricting pathogen within-host multiplication or between-host transmission rates. Thus, tolerance increases both host and pathogen fitness. Because of this two-sided effect, tolerance is expected to modulate host–pathogen coevolution and be a major determinant of the population dynamics of hosts and pathogens (66, 86). There is a large body of theory aimed at predicting the conditions in which tolerance is maintained in the host population and how pathogens evolve in response to host tolerance. Some of these studies focus solely on the evolution of either the host or the pathogen. Here, we review those studies in which the evolution of both interacting partners is simultaneously modeled and refer the reader to Pagán & García-Arenal (86) for a more extensive treatment of the topic.

Considering an endemic horizontally transmitted pathogen that causes permanent systemic infections in a long-lived host, Roy & Kirchner (113) predicted that any tolerance gene will tend to be fixed by selection in the host population, provided that the benefits of tolerance outweigh its costs. The rationale is that tolerance leads to higher pathogen prevalence, increasing the benefit of carrying the tolerance gene. Restif & Koella (106) expanded this model by incorporating costs of defense and attack strategies and assuming that virulence and transmission depend on both the host and the pathogen. Their analysis predicted that a host–pathogen interaction would reach an evolutionary stable state (ESS) at intermediate levels of host tolerance and pathogen multiplication. Also using an ESS approach, van den Bosch et al. (140) showed that tolerance puts pressure on the pathogen to evolve toward higher multiplication rates. Miller et al. (72) demonstrated that, considering the costs of tolerance and for parasites with a free-living stage, tolerance will evolve to fixation. Using this prediction as a starting point, they also demonstrated that if virulence decreases monotonically with tolerance, selection always results in increased pathogen multiplication. These highly exploitative pathogens would be more virulent in nontolerant hosts. However, if tolerance is less effective against pathogens with higher multiplication rates, selection for faster or slower replicating pathogens would occur depending on higher or lower transmission rates, respectively (73). Importantly, these models were valid for both mortality and fecundity tolerance. However, Best et al. (10) found that fecundity tolerance, but not mortality tolerance, led to host populations that are polymorphic for tolerance. This was because mortality tolerance had a positive effect on pathogen fitness, as it increases the infectious period, whereas fecundity tolerance did not impact pathogen fitness, and the host population could be polymorphic for fecundity tolerance. This conclusion does not apply to (*a*) vertically transmitted pathogens or (*b*) situations in which fecundity tolerance comes at the cost of a reduced host life span and therefore a shorter infectious period.

Following this argument, Vitale & Best (145) have shown that if mortality tolerance is costly, a reduction in tolerance may lead to pathogen extinction but not if it has no cost.

Support for these theoretical predictions comes mostly from analyses in wild systems in which both the host and the pathogen can evolve with no human intervention. For example, analyses in a dozen plant species of tolerance to *Puccinia* spp., *C. dematium*, or *E. fischeri* and in *M. guttatus* to CMV (9, 18, 19, 113, 130) showed low levels of genetic variation in fecundity tolerance, as predicted (72, 106, 113). Some of these experimental analyses showed larger genetic variation for the traits associated with tolerance in the absence of the pathogen than upon infection, suggesting pathogen selection for fecundity tolerance, which is against the assumption of neutrality proposed by Best et al. (10). This discrepancy could be explained, at least in part, by reported costs of tolerance for some of the above systems (9, 113, 130). However, a large variation in fecundity tolerance of *A. thaliana* to CMV (75, 83, 84) and TuMV (76) has been reported. Both viruses are seed transmitted in *A. thaliana* (24, 46, 87); thus, tolerance may have an effect on pathogen fitness (10). Although two of these studies (77, 83) analyzed a collection of *A. thaliana* genotypes representing the global genetic diversity of the host species, Montes et al. (75) analyzed the genetic variation of tolerance to CMV at the regional and local scale in the Iberian Peninsula, showing that tolerance polymorphisms occurred at the smaller spatial scales. Tolerance had a high heritability, and comparison of the genetic structure for tolerance with that for neutral markers indicated that tolerance is likely under uniform selection, which supports plant–virus coevolution. The role of tolerance in plant–pathogen coevolution is also supported by the results of a detailed study of *S. vulgaris* tolerance in the United Kingdom to two rust fungi, *C. tussilaginis*, which is native to the United Kingdom, and *P. lagenophorae*, which was recently introduced. As expected under the hypothesis of coevolution, tolerance to the native pathogen was higher than to the introduced fungus (49).

Evidence of pathogen evolution in response to host tolerance is only indirect. For example, in nine perennial shrubs showing tolerance to their host-specific rust fungi in a plant community, pathogen prevalence was high over a four-year period (114), which would agree with the Roy & Kirchner (113) prediction above.

Host–pathogen coevolution cannot be analyzed in agricultural settings, where the genetic composition of the host population is human-managed and only the pathogen population is allowed to evolve. However, models in which tolerance is considered as fixed in the host population (73) can be applied to this scenario, and the prediction of pathogen evolution toward higher virulence can be tested. The studies by Desbiez, Lecoq, and colleagues in Martinique showed that deploying zucchini cultivars tolerant to ZYMV resulted in the appearance of more virulent virus strains with an associated fitness penalty in nontolerant hosts (27–29), which is in agreement with the Miller et al. (73) predictions.

Thus, despite the importance of tolerance in understanding plant–pathogen coevolution, empirical and experimental tests of theoretical predictions of the effects of tolerance on the evolution of hosts and pathogens are still scant, and more research effort is needed in this area.

CONCLUDING REMARKS

For more than a century, research on the mechanisms of plant defenses against pathogens has been dominated by studies of resistance. Tolerance has received less attention, in part because of conflicting definitions and difficulties in its measurement. In this review, we underscore what is shared among the different definitions and analyses and attempt to make clear that tolerance is a plant defense strategy as effective and widespread as resistance. The experimental evidence indicates that tolerance has a significant impact on plant populations, allowing infected host individuals to survive and reproduce even as efficiently as noninfected hosts. Tolerance can

prevent plant population extinction at high pathogen prevalence. Tolerance also affects pathogen epidemiology by increasing pathogen prevalence, which in turn increases the advantage of tolerant host genotypes. This feedback loop is expected to affect the genetic composition of the host and pathogen populations, although this subject remains underexplored. Tolerance is also predicted to affect pathogen evolution by inducing changes in virulence and multiplication rates. Increasing awareness of the relevance of tolerance to pathogens has led to the proposal that tolerance could be a successful strategy to control pathogen outbreaks in agricultural settings when resistance has not been described, is difficult to breed for, or is quickly overcome by the pathogen. Thus, tolerance has great potential in plant disease control and is of great relevance to understanding host–pathogen interactions in wild plant populations.

FUTURE ISSUES

1. Attention should be paid to the different ways of quantifying tolerance and how results are affected by the selected procedure. This should provide guidelines to choose the most appropriate metric according to the research goals.
2. Studies of the genetic basis of tolerance are needed across a larger range of plant–pathogen systems, and at higher genomic resolution, to better understand the mechanisms of tolerance, its potential in crop breeding, and its role in plant–pathogen coevolution.
3. Studies are needed to understand the molecular bases of tolerance and how they translate into life-history trait modulation resulting in tolerance.
4. The effects of environmental heterogeneity on tolerance expression and function require further research effort, particularly from a multifactorial perspective.
5. The role of tolerance in plant–pathogen coevolution should be analyzed experimentally, and the predictions of theoretical models should be tested with the resulting data.

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