Title

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Publication Date

2016-07-01

DOI

10.1016/j.pmpp.2016.02.004

Peer reviewed

Physiological and Molecular Plant Pathology 95 (2016) 55–59

Contents lists available at ScienceDirect

Physiological and Molecular Plant Pathology

journal homepage: www.elsevier.com/locate/pmpp

False idolatry of the mythical growth versus immunity tradeoff in molecular systems plant pathology☆

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ARTICLE INFO

Article history:
Received 21 December 2015
Received in revised form
3 February 2016
Accepted 5 February 2016
Available online 10 February 2016

Keywords:
Growth
Immunity
Tradeoff
Systems biology
Plant pathology

ABSTRACT

Systems studies of signal transduction pathways that modulate plant growth and immunity are rapidly identifying a large number of interactions within these pathways. These interactions are frequently presented as mechanisms allowing a plant to make proper decisions with regards to how to partition energy and resources in a proposed growth versus immunity tradeoff. This is a reinterpretation of the classical costs of resistance theory that has a long history in the ecology research community. While the ecology community is reinterpreting this theory, the reinterpretation has not been introduced into the molecular systems biology community that is studying the intersection of regulatory pathways. In this article, I describe evidence against a simple growth versus immunity tradeoff concept and propose an alternative wherein the intersection of these regulatory pathways is instead designed to coordinate these pathways, and not simply link them in mutual antagonism, to optimize fitness in complex environments where resistance/immunity and growth do not have simple linear relationships with fitness.

1. Introduction

Recent years have seen the re-introduction of ecological theories into studies focused on molecular plant pathology. This includes a burgeoning interest in the concept of costs of resistance and how this may drive an interplay between growth and immunity [1,2]. A cost of resistance is broadly defined as any negative effect that expressing a resistance trait has on plant fitness [2–5]. In plant pathology, this is being increasingly linked to an interest in tradeoffs between growth and immunity [6–14]. This is being driven by molecular studies that are finding interactions between regulatory genes involved in the control of growth and defense. These links are being found in related signaling pathways that interlink the brassinosteroid and effector triggered immunity pathways [7,11,12,15]. Similar links between development and plant defense signaling have been found for gibberellins, salicylic acid, auxin and jasmonic acid [16–22]. Interestingly, just as the molecular plant pathology community is beginning to investigate their systems using a cost of resistance framework, the ecology community is reassessing if there are costs of resistance and what this concept fundamentally means [3–5]. However, this reconsideration in the ecological community has not yet been translated into studies of molecular plant pathology. This article is intended to communicate misperceptions about costs of resistance that are permeating the molecular oriented literature and to provide alternate concepts of what is truly meant by the cost of immunity.

2. What do flux costs mean in a natural context?

The most common interpretation of resistance costs makes the implicit assumption that energy and elements are universally limiting for plant growth and/or fitness in the wild [13,14]. This is often pictorialized as a teeter-totter wherein the plant has to decide if any specific element or energy is placed into growth or defense. This simplistic representation also makes the implicit statement that there are no other options or avenues open to the plant in this process. This teeter-totter model can be classified as the idea that any flux of a nutrient into a defense process necessarily removes that nutrient from what otherwise would have been growth or biomass accumulation, i.e. a flux cost model (Fig. 1). However, the way the flux cost model is presented assumes that all nutrients are equally limiting which is an oversimplification of how nutrients limit plant fitness in the wild [23]. In natural ecosystems, growth is limited by imbalances in the availability of nutrients and

☆ This article is part of a special issue entitled "The U.S.-Japan Scientific Seminar: Molecular Contact Points in Host-Pathogen Co-evolution".

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http://dx.doi.org/10.1016/j.pmpp.2016.02.004
0885-5765/

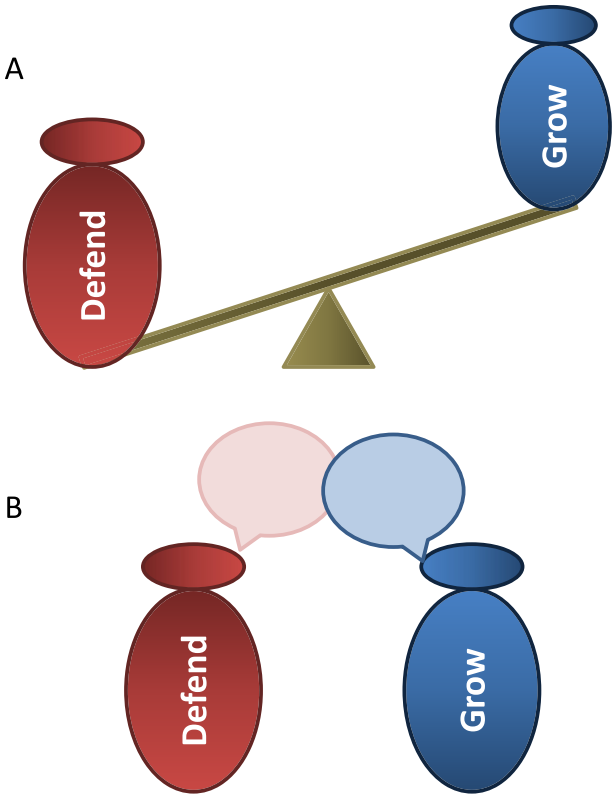

Fig. 1. Alternative models of growth and defense. A. Standard illustration of the growth vs immunity tradeoff where the two are in opposition. B. Alternative conceptualization whereby growth and defense are in a continual conversation to coordinate.

micronutrients rather than singular nutrient limitations. This means that potassium or phosphorus may be growth limiting in an environment where carbon and nitrogen may be freely available and non-limiting [23]. As such, it is the balance of nutrients that is more critical than any single nutrient when considering how nutrients may limit growth.

The observation that the plant is more responsive to the specific balance of nutrients and micronutrients raises the possibility that nutrient limitations on growth may be different than nutrient limitations on defense. Most plant defense mechanisms are based on proteins and metabolites that are predominantly Carbon and Nitrogen based with almost no associated Potassium and Phosphorus [24–26]. Thus, it is possible that in environments where Potassium, Phosphorus or other micronutrients are growth limiting that the plant has spare Carbon and Nitrogen available that cannot be used for growth. This spare Carbon and Nitrogen could then be used to create defenses at essentially no cost to growth. Thus, flux costs are not universal and instead are highly conditional based on the available nutrient and energy status of the plants environment. This suggests that the specific defense metabolism and mechanisms in a plant may be co-adapted to the plants typical nutrient profile to maximize the utilization of nutrients that are not rate limiting in that plants ecosystem niche. For example, a plant that typically grows in nitrogen limiting environments may shift from nitrogen-heavy defenses like alkaloids towards carboniferous defenses like terpenoids.

3. But constitutive defense mutants grow smaller?

A common argument in support of the idea that growth and defense must be in a tradeoff relationship is the observation that constitutive defense mutants are frequently small [27–32]. This argument posits that the elevated defense in these mutants is removing nutrients that would otherwise be utilized for growth. However, there is little evidence about the exact molecular reason for the diminutive growth in these mutants. A similar growth defect argument was proposed to explain why the *reduced epidermal fluorescence* (*ref*) mutants deficient in phenolic metabolism displayed growth defects [33–36]. It was posited that the deficiency in lignin production and structure created a simple growth defect due to altered lignin physics [33–36]. However, this was later found to be an incorrect interpretation as shown by a suppressor screen that identified mutants that alleviated the growth defects in the *ref* mutants [35,37–39]. These suppressors had wild-type growth rates while still containing the deficient lignin indicating that the growth effect was not caused by physical issues associated with the lignin deficit. Instead all of the suppressor mutations were in genes encoding components of the mediator transcriptional complex showing that the growth defect was caused by altered signal transduction and regulation of development and not by the physical or flux based costs of the *ref* mutant [35,37–39]. Thus, it is possible that mutants displaying constitutive defense responses may show a growth defect for regulatory or developmental reasons that have nothing to do with the associated flux cost of producing those defense responses. For example, constitutive expression of jasmonate mediated defenses didn't specifically alter growth but instead altered flowering time and other phenological processes suggesting that this constitutive jasmonate mutant displayed regulatory costs more than elemental costs [40]. Thus, more work needs to be done to understand why constitutive defense mutants display growth defects.

Modern biochemical genetics is providing a more explicit assessment of the flux costs associated with specific defenses by providing the ability to genetically delete individual defense genes or pathways and then assess any resulting growth effect. The simple growth vs immunity tradeoff model would suggest that the energy no longer used for defense in these mutants should be redirected from into growth. Analysis of genotypes altered in glucosinolate accumulation was unable to find a significant link with absolute growth [41–43]. Instead, it was only possible to see a small increase in relative growth rate in these mutants and only at early developmental stages and not in larger mature plants [41,42]. Importantly, this slight growth rate boost only benefited these plants when they are competing with other plant genotypes, i.e. a low glucosinolate plant would outgrow a high glucosinolate plant when they are in direct competition. Similar results had been found in the wild using Brassica [44–46]. Thus, if there is a direct growth benefit obtained by redirecting defenses to growth, these benefits appear to be specific to conditions when two genotypes are in direct competition. Thus, studying any growth vs immunity tradeoff hypothesis must involve competition studies.

4. What are other costs of immunity/resistance?

The experiment showing potentially the most overt cost of a resistance mechanism was a set of studies that linked the presence of an R gene to a fitness cost in the absence of the pathogen [47–49]. This study was originally controversial because the estimated flux cost, the energy required to produce a single R gene encoded protein that accumulates to low levels, did not agree with the measured 9% cost in fitness in plants expressing the functional R protein [48]. However, flux costs are not the only potential cost for a resistance mechanism. There are also ecological or opportunity costs wherein a resistance mechanism that may provide a fitness benefit by aiding the plants interaction with one organism

may actually create a cost by decreasing the plants ability to interact with another organism [44–46,50,51]. In this particular case, an ecological cost hypothesis could be as simple as the presence of the R gene may have altered the microbiome of these plants leading to the decreased fitness. Resistance signaling genes have been found to specifically affect the plants associated microbiome supporting this potential ecological cost [52,53]. Another possibility is that this specific R gene actually generates sensitivity to an unknown pathogen as has been found for the LOV1 locus [54–58]. In this case, the cost or benefit of the R gene would depend upon the presence or absence of the respective species within the plants environment. Supporting the potential for ecological costs in a broader context is work on defense metabolites linking them to a number of detrimental side effects depending upon the specific insect community in which the plant exists [59–62].

Supporting the concept that ecological costs may be more important than flux costs, the authors utilized a set of R gene isogenic lines to assess how plant fitness responded to infection with the pathogen in the presence or absence of competition with uninfected plants [49]. In the presence of competition by uninfected plants, the ability to resist the pathogen increased a plants fitness. Interestingly, when the plants were grown in the absence of other plants (no competition) there was no fitness benefit provided by the R gene and the associated pathogen resistance. If anything, the R gene led to decreased fitness in the presence of the pathogen [49]. In this case, the susceptible plants were able to compensate for the infection by increasing their seed production on secondary inflorescences. Thus, depending upon the organisms present within an environment, a specific resistance mechanism can invert from being costly to being beneficial. In this case, susceptibility to a pathogen was beneficial to plant fitness under specific conditions [49]. The ability of fluctuations in the environment to shift the fitness effect of specific resistance mechanisms has also been seen for defense metabolites [63]. Thus, the environment can impart ecological fitness costs that vastly outweigh any potential flux cost. Importantly, this also shows that it is not possible to classify all defenses as a single group when developing a model linking development to immunity.

5. For what other reasons could development and immunity be linked?

If flux costs of resistance are not the driving force behind the observed link between growth and immunity, this raises the question of what would be other reasons for these two processes to be linked. The growth vs immunity tradeoff concept fundamentally imagines growth and immunity as opposing contretemps in a zero sum game where for one to increase, the other must necessarily decrease. This is however, a misreading of the relationship between development and resistance. An alternative interpretation is that properly structured development is a key component of resistance. For example, shifting flowering time is a potentially effective way for plants to resist specific foliar herbivores by allowing the plant to evade these herbivores as seeds. Similarly as shown above, plants can alleviate the effects of a plant/pathogen interaction by a developmental reprogramming that increases the production of secondary inflorescences to compensate [49]. Developmental compensation is also a major mechanism that relieves deleterious consequences of plant herbivore interactions [64–66]. As such, major morphological shifts in development can be key aspects of how a plant interacts with other organisms.

Another facet of the interplay between growth and defense that is often overlooked by the growth vs immunity tradeoff concept is that defense mechanisms are not ubiquitously distributed across a whole plant but are instead placed in specific locations for potentially specific reasons. In these instances, an explicit intersection of immunity and developmental pathways is central to placing defenses in their proper whole organism context to maximize their utility. This includes placing defense metabolites in specific structures like laticifers and glandular trichomes or enhancing pathogen defenses by elevating their expression in stomata [67–69]. While the specific developmental patterning of defenses can be thought to place them in the proper location for optimal function, there are other potential reasons for this patterning. The developmental patterning of anti-herbivory defenses in Arabidopsis actually affects the feeding behavior of the lepidopteran herbivores [70,71]. This raises the possibility that the specific pattern could be a part of the defense activity by potentially leading the herbivore to a detrimental feeding behavior that may maximize its exposure to predators or parasites [72]. Another potential benefit from distributing defenses unequally across a specific tissue is that this patterning may decrease the ability of the attacking organisms to evolve a counter-defense strategy [73,74]. This suggests that it is better to view development and immunity as two processes that are coordinated to optimize a plants interaction with its environment and not as opponents in a zero sum game.

6. Summary

Growth (development) and immunity (resistance) are highly interlinked processes as exemplified by the increasing evidence for cross-talk in the different pathways. While this has begun to be described as a tradeoff relationship between growth and immunity locked in a zero sum game, the above studies and observations illustrate that this is likely a misreading of the growth to immunity relationship within a plant. Instead, we need to develop a deeper conceptualization of the link between growth and immunity wherein the two are integrating, sometimes as a tradeoff and other times synergistically, to maximize the plants ensuing fitness depending upon the specific environment in which that plant exists (Fig. 1B). It is only by developing this more conditional and realistic framework in which to study the connections between growth and immunity that we will make full progress in understanding how plant fitness is maximized in the wild.

Acknowledgments

Funding for this work was provided by the NSF awards IOS 1339125 and MCB 1330337 to DJK, the USDA National Institute of Food and Agriculture, Hatch project number CA-D-PLS-7033-H to DJK, and by the Danish National Research Foundation (DNRF99) grant to DJK.

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