The Genetic Basis of Plant-Herbivore Interactions

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Learning Objectives

This chapter will help readers to understand the following:

1. How advances in genetic technology have affected the study of plant-herbivore interactions
2. The prevalence of genetic variation in herbivory resistance traits in natural plant populations
3. Assessment of natural selection by herbivores in plant populations
4. Ways in which hypotheses for the evolution of plant defenses can be tested at a genetic level
5. How studies of gene expression can inform our understanding of plant-herbivore interactions

4.1 Introduction

A large proportion of global biodiversity and biomass consists of plants and their herbivores. Invertebrate herbivores such as insects, and vertebrate plant browsers such as deer and other mammals, consume plant tissue and impose a strong selective pressure on plants that has been ongoing for millions of years. Fossil evidence suggests that insects, for example, have been feeding on plants for an estimated 400 million years (Labandeira 2013; Bruce 2015). The evolutionary relationship between insects and their host plants is discussed in Ehrlich and Raven (1964), a now classic work that has received more than 2500 citations to date. Plants have evolved to produce a great diversity of defenses to resist herbivory (Hanley et al. 2007; Erb et al. 2012; Rasmann and Agrawal 2009). Phytochemical defenses are key among these defenses and are present in all higher plants in a wide variety of form and function (Fraenkel 1959; Wink 2003). The importance of *co-evolutionary* relationships, or reciprocal evolutionary interactions between herbivores and plants, in the evolution of both plants and herbivores has since been highlighted many times, at both macroevolutionary (e.g., Becerra 1997) and microevolutionary (e.g., Mauricio and Rausher 1997) scales.

At a macroevolutionary scale, phytochemicals can play a key role in the evolution of host shifts by herbivorous insects. For example, a molecular phylogenetic study in the plant genus *Bursera* and the beetle genus *Blepharida* shows that the patterns of host shifts in *Blepharida* beetles are strongly associated with patterns of host phytochemical similarity in the *Bursera* genus (Becerra 1997). The interaction between these beetles and plant genus is specialized and is evolutionarily old. The plants produce a variety of terpenes that are present in resin canals in the plant leaves and stems and decrease *Blepharida* survival and growth rate (Becerra and Venable 1990).

At the microevolutionary scale, there is abundant evidence that herbivory reduces plant fitness, and that herbivores are agents of natural selection on plant resistance traits (Marquis 1992; Núñez-Farfán and Dirzo 1994; Sagers and Coley 1995; Fornoni et al. 2003). For example, in *Arabidopsis thaliana*, the elimination of herbivores in a field experiment altered the pattern of selection on two defense

traits, glucosinolate concentrations and trichome density (Mauricio and Rausher 1997). Likewise, herbivore-mediated natural selection was detected on stereochemistry of the secondary metabolites, sesquiterpene lactones, of common cocklebur (*Xanthium strumarium*). In natural environments, plants with cis-fused lactone ring junctions received higher levels of herbivory than those with trans-fused lactone ring junctions; herbivore damage was negatively correlated with plant fitness (Ahern and Whitney 2014). Finally, an assessment of selection imposed by both *generalist* and *specialist* herbivores (those with greater versus lesser dietary host breadth) in *Datura stramonium* demonstrated that generalists and specialists can impose divergent selection pressures on host plant resistance traits (Castillo et al. 2014). Geographic variation in herbivore community composition can thus lead to differences in resistance among populations across a plant species range.

4.2 Types of Resistance Traits

Plant defenses against herbivory include resistance, tolerance, and temporal avoidance. Resistance traits reduce the performance and/or preference of herbivores, while tolerance is a measure the extent to which plant fitness is affected by herbivory, relative to fitness in the absence of damage (Strauss and Agrawal 1999). In this chapter, I focus on plant resistance traits, and use "resistance" and "defense" interchangeably.

Plant *secondary compounds* are metabolites that do not play a role in the growth and development of the plant (Fraenkel 1959; Berenbaum and Zangerl 2008; but see Erb and Kliebenstein 2020). Hundreds of thousands of secondary compound structures have been elucidated, with many others yet uncharacterized (Wink 1988; Pichersky and Lewinsohn 2011). Secondary compounds can be toxic, anti-nutritive or anti-digestive, and/or act to repel herbivores through low palatability (Mithöfer and Boland 2012). These phytochemicals are highly structurally diverse, and include classes such as phenolics, terpenoids, and alkaloids, among others (Harborne et al. 1999; Wink 2018). Some secondary compounds, such as lignin, are more generalized defenses that affect many types of herbivores (Franceschi et al. 2005). Others, such as many alkaloids, have specific targets- enzymes or nucleic acids, for example- that they interact with in an herbivore (Mithöfer and Boland 2012). Secondary compounds can act individually or interactively to deter herbivores (Mason and Singer 2015).

There is often consistency in broad patterns of classes of compounds across closely related taxa (Wink 2003; Liscombe et al. 2005), but this consistency, or phylogenetic signal, is not always strong. Divergence in phytochemical defenses can occur through the evolution of novel compounds and/or the evolution of novel combinations of compounds. For example, in the wild parsnip system, plants escape from adapted herbivores by producing ecologically novel compounds, often from the same chemical precursor (Berenbaum 1978, 1983). Alternatively, in the tropical plant genus *Inga*, closely related species produce different combinations (and presence/absence patterns) of commonly produced compounds (Coley et al. 2018).

While much of the literature focuses on phytochemical traits, there are numerous, complex plant defenses that have evolved in response to herbivory, including *physical defenses*. Physical defenses are structural deterrents that impede the ability of herbivores to feed on the plant, and include traits such as toughened leaves, spines, thorns, or trichomes (hairlike extensions from the plant epidermis), or the incorporation of hard materials such as silica into the foliar tissue (Hanley et al. 2007). Thorns, spines, and trichomes can be present in many forms, and some trichomes produce glandular exudates that are toxic or can trap or repel herbivores (Levin 1973; Elle and Hare 2000; Hauser 2014). Trichome glandular exudates often contain secondary compounds, thus merging physical and chemical resistance (Glas et al. 2012). An example of this latter phenomenon is with stinging nettle (*Urtica dioica*), where the trichomes contain secondary compounds that are released by contact and confer a stinging sensation to mammals (Pollard and Briggs 1984). While they are overlooked in the literature to a much greater extent than phytochemical resistance traits, physical resistance traits have been clearly shown to be effective against herbivory (Mauricio 1998; Hanley et al. 2007; Barton 2016).

Resistance to herbivory can occur through *direct defenses*, which make the plant a less suitable host due to changes in physical or phytochemical defense traits, or *indirect defenses*, through which plants reduce levels of herbivory by interacting with herbivore enemies (Heil 2008; Pearse et al. 2020). Indirect defenses include the induction of volatile compounds that attract parasitoids and predators (Dicke 1999; Dicke and Hilker 2003), and traits that provide shelter, food, or other incentives to predators (Heil et al. 2001; Heil 2008; Weber and Agrawal 2014; Weber et al. 2016).

4.3 Temporal and Spatial Variation in Resistance Traits

Perhaps in part because of the sessile nature of plants, plant defenses are not static over time or across plants. Plants may produce direct and indirect defenses *constitutively*, in the absence of herbivory or regardless of levels of herbivory; alternatively, plants also *induce* defenses through plastic changes in levels of defense following herbivory (Adler and Karban 1994; Agrawal 1998; Cipollini 1998; Karban et al. 1999). Induction of defenses can be selected for if past/current herbivory is a reliable predictor of future herbivory, and if herbivory decreases plant fitness (Karban and Baldwin 1997; Harvell and Tollrian 1999). Plants can also plastically alter the availability of essential amino acids and nutrients available for digestion by the herbivore (Chen et al. 2005; Felton 2005). In addition to induction of defense within a plant generation, defenses can also be *transgenerationally induced*, whereby offspring defense phenotypes are altered by environmental signal in the parental generation and expressed independently of changes in the offspring genotype (Holeski et al. 2012b). This transgenerational induction can occur via *epigenetic* or maternal effects (Richards 2006; Roach and Wulff 1987). Epigenetic effects are heritable changes in traits that are mediated by mechanisms other than

alterations in the DNA sequence, such as DNA methylation and histone modification (Rapp and Wendel 2005; Hauser et al. 2011).

Both constitutive and induced resistance can change as plants develop (Boege and Marquis 2005; Barton and Koricheva 2010; Holeski et al. 2012a). True leaves from different developmental, or *ontogenetic*, stages (e.g., juvenile versus adult) are usually anatomically and biochemically different, with different patterns of cellular differentiation (Poethig 1997; Mauricio 2005). The direction of change in resistance traits across ontogenetic stages is variable; some species have higher levels of resistance in the juvenile developmental stage relative to the adult (Price et al. 1987; Kearsley and Whitham 1989; Cole et al. 2020), while others have increased resistance in the adult developmental stage relative to the juvenile (Karban and Thaler 1999).

Finally, levels of defense can change in a predictable manner across the course of a growing season. These temporal changes in (usually phytochemical) defense are likely in part due to shifting allocational priorities, for example between defense, growth, and reproduction) as leaves age, as well as dilution as leaves expand. Physiological changes across a season can also affect defense concentrations, and are caused by shifts in photoperiod, temperature, and water and nutrient availability (Darrow and Bowers 1997; Holeski et al. 2012a; Koricheva and Barton 2012).

4.4 Evolution of Plant Resistance Hypotheses

Many hypotheses have been developed to explain how patterns in defense production within and across populations or closely related species may have evolved. Prominent among these are the Resource Allocation Hypothesis (RAH; Coley et al. 1985) and Optimal Defense Theory (ODT; Rhoades 1979).

The Resource Availability Hypothesis (RAH) hypothesis was formulated specifically for inter-species differences in plant defenses, while Optimal Defense Theory (ODT) is typically used to describe intra-species differences. Both are testable hypotheses. The RAH posits that defense investment is dependent on growth rate; long-lived species invest more heavily in defenses than do short-lived species, due to the cost-benefit ratio of the defense investment (Coley et al. 1985; Endara and Coley 2011). This hypothesis assumes that shorter life cycles are synonymous with rapid growth rate, so that the negative impact of losing leaf area is low in these species (Endara and Coley 2011). The RAH has since been extrapolated to an intra-species context (Hahn and Maron 2016; López-Goldar et al. 2020).

Three basic predictions of ODT (Rhoades 1979; Herms and Mattson 1992; Koricheva 2002; Stamp 2003) are that, first, plants will evolve a level of defense that is positively related to rates of herbivory and negatively related to allocational or ecological cost. Second, plants will differentially allocate defense to different parts or tissues, with greater investment in tissues with high fitness values or where the cost of defense is lower. Third, plants will increase defense in response to attack, a form of plasticity that is often referred to as induction. ODT predicts that the capacity for induction should be negatively correlated with levels of constitutive defense.

While hypotheses about the processes governing allocation of resources to plant defense differ, one common thread in contemplating the *evolution* of defense production within or across natural plant populations is the genetic basis of defenses. *Genetic variation* in traits within a plant population, or differences among individuals in DNA sequence of genes that underlie focal traits, is a necessary prerequisite to evolution. Historically, the study of plant defense traits has focused on phenotypic variation. As molecular genetic tools and knowledge gained from use of these tools have continued to develop, an increasing number of studies are directly assessing genetic-based patterns of trait production and trade-offs between traits. This work has provided insight into the genetic mechanisms behind the phenotypic patterns of defense trait evolution that we observe, as well as information about the evolutionary potential for plant resistance traits. Evolutionary/ecological hypotheses for patterns of defense trait production, among them the Research Allocation Hypothesis and Optimal Defense Theory, were developed when understanding of the genetic underpinnings of traits was not well understood. Studies of genetic variation during that era were at the level of protein electrophoresis. Testing these hypotheses at the level of genes or genetic correlations, rather than phenotypes and phenotypic correlations, was unprecedented 30–40 years ago (◘ Fig. 4.1).

4.5 Microevolution of Plant Resistance

While decades of research have provided us with valuable information about defense phenotypes, microevolutionary inferences from these studies were limited until studies with the power to elucidate differences in plant defense among genotypes began in the 1980s (e.g., Berenbaum et al. 1986). In total, the relatively large body of work investigating genetic variation in resistance traits indicates it is widespread across both herbaceous and woody plant species (Stowe 1998; Moore et al. 2014).

4.5.1 Direct Defenses

While many studies demonstrating genotypic or genetic variation are done in herbaceous plants, due to ease of experimentation, woody plants also show substantial variation among genotypes in resistance traits, as showcased in multiple studies of *Populus* species (e.g., Havill and Raffa 1999; Lindroth and Hwang 1996; Holeski et al. 2012a; Cope et al. 2019). This work has also highlighted the interaction between genetics and the environment in influencing defense phenotypes. For example, in quaking aspen (*Populus angustifolia*), concentrations of phenolic glycosides, a phytochemical defense, vary substantially with genotype. Environmental factors such as light and nutrient availability also (significantly) affect phenolic glycoside concentrations, and do so differently among genotypes, but genotype is the dominant influence on variation in this trait (Osier and Lindroth 2001, 2004, 2006). In contrast, another phytochemical resistance trait, condensed tannin concentrations, is quite plastic, with variation in the trait typically influenced primarily

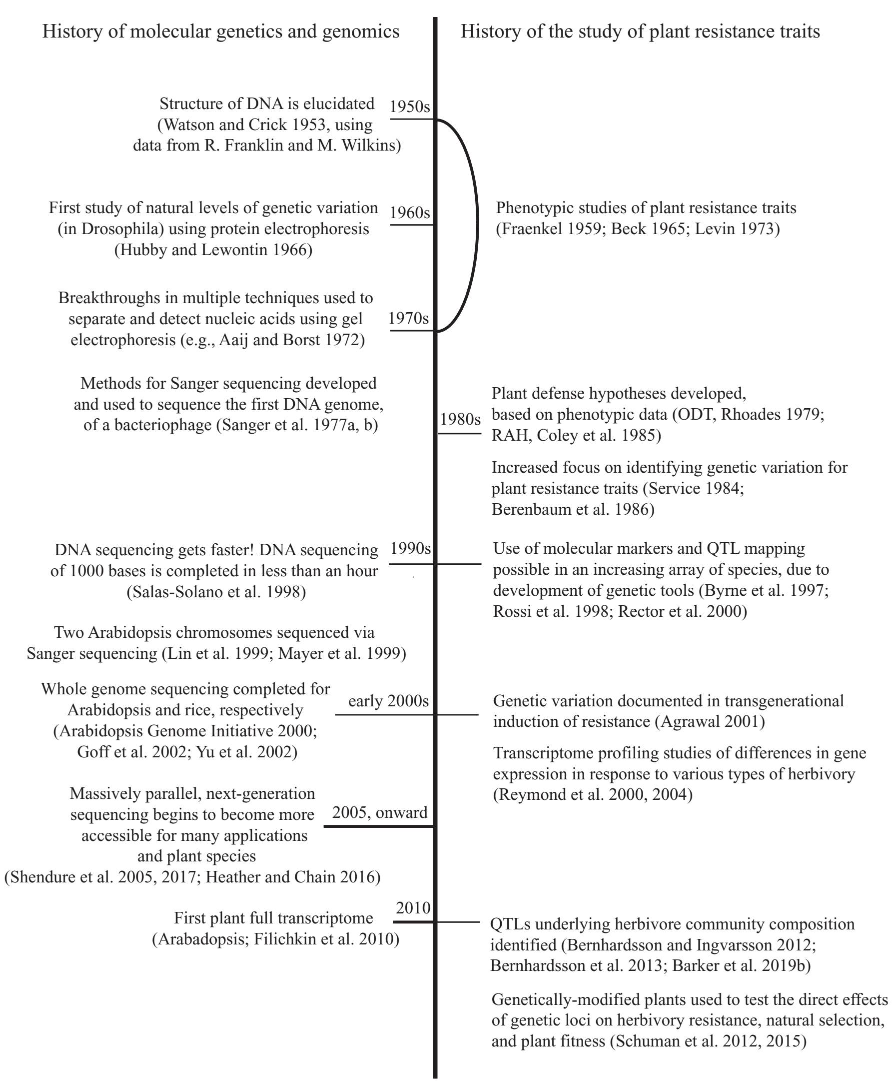

Fig. 4.1 Timeline of advances in development of genetic and genomic technology (left panel) and of genetic understanding of plant-herbivore interactions (right panel)

by environmental factors such as light availability, or tissue defoliation, rather than genotype (e.g., Hemming and Lindroth 1995; Osier and Lindroth 2004, 2006). *Genotype-by-environment interactions*, whereby individuals of the same genotype respond to an environmental factor differently in terms of plastic trait expression (e.g., Barker et al. 2019a; Fig. 4.2) also influence condensed tannin concentrations in aspen, albeit to a lesser extent than particular environmental factors (Osier and Lindroth 2006). Ontogenetic trajectories of some resistance traits in cottonwood (*Populus fremontii, P. angustifolia*, and their hybrids) have also been shown

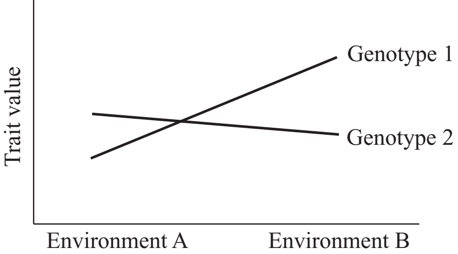

Fig. 4.2 Genotype-environment interactions schematic. Genotype 2 has a higher trait value in Environment A, relative to Genotype 1. Genotype 1 has a higher trait value in Environment B, relative to Genotype 2

to have a genetic basis (Rehill et al. 2006; Holeski et al. 2012a; Cope et al. 2019). Research in another woody plant genus, *Eucalyptus,* has similarly found genotypic variation in resistance to mammalian browsers (O'Reilly-Wapstra et al. 2002, 2004, 2005). Genetic variation exists between different natural populations of *E. globulus* for resistance to browsing by a generalist marsupial, *Trichosurus vulpecula* (common brushtail possum). As in *Populus*, ontogenetic trajectories of at least some resistance traits are genetically-based in *E. globulus* (O'Reilly-Wapstra et al. 2007).

Research in multiple species illustrates that intra-specific genetic variation (Dungey et al. 2000; Gosney et al. 2014, 2017) as well as genotypic variation (Fritz and Price 1988; Underwood and Rausher 2000) can affect herbivore population dynamics and/or herbivore community composition. It should be noted, however that genetic variation in resistance traits is often not measured in these studies, and the mechanism behind the effects of host genetic variation on herbivores is not always known. Studies of the influence of genotypic variation on herbivore communities that do incorporate genotypic variation in resistance traits includes those in both herbaceous plants (*Arabidopsis thaliana*, Sato et al. 2019a; *Oenothera biennis*, Johnson and Agrawal 2005, 2007) and woody plants (*Populus sp.,* Wimp et al. 2007; Keith et al. 2010; Robinson et al. 2012; Barbour et al. 2016; Barker et al. 2018). Several of these experiments show that while genotypic variation in plant resistance traits does have some effect on arthropod community composition, community composition is most strongly associated with genotypic variation in other traits such as plant size, architecture, and phenology (e.g., Johnson and Agrawal 2005; Robinson et al. 2012; Barker et al. 2018).

4.5.2 Natural Selection on Herbivory Resistance

In addition to genetic variation for a trait, the trait must be acted upon by natural selection (or drift) in order to evolve within a population. Rausher (1996) succinctly described three necessary points for demonstrating that herbivores impose natural selection on resistance traits in their host plants. First, one must show that genetic variation for the focal resistance traits exists. Second, the resistance traits must be demonstrated to be under natural selection. This might be done by showing that genotypes that differ in resistance also differ in fitness. Third, natural herbivores should be manipulated in presence/absence or in density, so that selection on resistance traits can be assessed across treatments. This latter point

allows the effects of herbivory to be disentangled from other environmental factors, and thus prevents selection on correlated traits from being confused with selection on resistance.

Several elegant studies in the 1980s–1990s completed these steps to demonstrate that herbivores do impose natural selection on plant resistance traits. One comprehensive set of manipulative field experiments showing both genetic variation in resistance and natural selection acting on resistance was in morning glory (*Ipomoea purpurea*). In one field experiment, genetic variation for resistance to specialist flea beetles (*Chaetocnema confinis*) was found under ambient levels of herbivory (Simms and Rausher 1987). In complementary experiments that manipulated levels of herbivory into ambient versus no herbivory via an insecticide spray, additive genetic variation for resistance to both specialist and generalist herbivores was detected, as well as natural selection acting on this resistance (Rausher and Simms 1989; Simms and Rausher 1989). Another study meeting the stringent criteria outlined by Rausher (1996) was done in jimson weed (*Datura stramonium*). The two major alkaloids in *D. stramonium* were found to be under negative directional selection and stabilizing selection, respectively, with insect herbivores as the agents of selection (Shonle and Bergelson 2000).

4.5.3 Indirect Defenses

While it is often inferred that indirect defense traits increase plant fitness if they reduce herbivore damage, the effects of indirect defenses on plant fitness are rarely directly demonstrated. Exceptions include an experimental study of leaf domatia, small hair-tufts or pockets, in cotton (*Gossypium hirsutum*; Agrawal and Karban 1997), and work on extrafloral nectaries and ant-plant associations in wild cotton (*Gossypium thurberi*; Rudgers 2004; Rudgers and Strauss 2004) and in partridge pea (*Chamaecrista fasciculata*; Rutter and Rausher 2004). In the latter example, there was evidence of costs of nectar production for plants in the absence of ants, and these costs were heightened by herbivory. When ants are present, however, natural selection favored high extrafloral nectar production (Rutter and Rausher 2004).

4.5.4 Transgenerational Defense

As with within-generation defense, the evolutionary relevance of transgenerational induction in defenses is contingent upon whether there is genetic variation, as well as the impacts of transgenerational induction on plant fitness (Kalisz and Purugganan 2004; Richards 2006; Day and Bonduriansky 2011). Genetic variation in transgenerational induction of defense has been shown in multiple species, including wild radish, monkeyflower, and dandelion (Agrawal 2001, 2002; Holeski 2007; Verhoeven et al. 2009; Colicchio 2017). Very few studies have incorporated an experimental design allowing both genetic variation for transgenerational plasticity of defense and the effects on traits related to organism fitness to be examined

outside of a laboratory or greenhouse environment (Agrawal 2001, 2002; Holeski et al. 2013), and no published study has measured natural selection on transgenerational plasticity of defense.

Transgenerational plasticity in resistance has been demonstrated to affect plant fitness in natural conditions, although the rare studies investigating fitness have not also assessed genetic variation. In wild lima bean (*Phaseolus lunatus*), offspring of plants that experienced experimentally elevated levels of Chrysomelid beetle herbivory and offspring of control plants that experienced ambient herbivory were assessed in a field environment. Offspring of the elevated-herbivory plants showed higher levels of constitutive resistance traits in the seedlings and juvenile stages, as well as higher survival rates as seedlings (Ballhorn et al. 2016). Work in Carolina horsenettle (*Solanum carolinense*) demonstrates that the offspring of herbivore-damaged plants have decreased time to flowering, and/or produced more flowers than the offspring of control plants (Nihranz et al. 2020).

In summary, while research in both herbaceous and woody plant systems illustrates that genetic variation in resistance traits is widespread, comprehensive studies of the portion of genetic variation that selection acts upon, additive genetic variation, as well as investigation of natural selection on these traits is labor-intensive and is still relatively rare. In most cases, the ecological and evolutionary processes creating and maintaining the genetic variation and how they interact with the genome is still unclear. However, advances in genetic and genomic technology are allowing us to begin to elucidate these interactions, through identification of how genes underlying resistance traits are structured, as well as how genes affect the ecological interactions of plants.

4.6 Identification of Genes Underlying Resistance

4.6.1 Genetic Mapping

As the power to conduct genetic analyses developed, a number of studies in different plant species conducted genetic mapping experiments to identify genetic regions (*quantitative trait loci* or *QTL*) underlying defense trait variation; this technique can be followed by fine-scale mapping to identify specific genes within those regions (Doerge 2002). In plant species with short generation times that can be crossed with reasonable ease, genetic mapping can be done through controlled crosses of individuals divergent for the trait(s) of interest and QTL genetic mapping. Traditional QTL mapping is a labor-intensive process that involves phenotyping large numbers of individuals for traits of interest, in addition to molecular genetics work to genotype individuals at a number of *genetic markers*. Genetic markers are single nucleotides or small regions of the genome that are typically non-coding. Genetic markers are thus not directly involved with producing the trait of interest but may be linked to genes that do underlie these traits. QTL mapping is done through statistical techniques that associate presence of genetic variants (sequence variation, or different marker genotypes) to phenotypic variation in

the traits of interest. Genetic markers that are linked to genes influencing the trait of interest will show non-random statistical associations between marker genotype and a particular phenotype. QTL mapping ultimately tells us the amount of observed phenotypic variation in a trait that can be explained by a particular genomic region (Falconer and Mackay 1996; Lynch and Walsh 1998).

In plants with long generation times or those are not amenable to controlled crosses, other techniques such as *genome-wide association mapping* (*GWAS*), also called linkage disequilibrium mapping, are often used (Stinchcombe and Hoekstra 2008; Hall et al. 2010). These studies require a study system in which application of next-generation sequencing technology is feasible (a rapidly increasing number of species) and have a number of logistical advantages over traditional QTL mapping (Table 4.1; Nordborg and Weigel 2008; Hall et al. 2010; Ingvarsson and Street 2011).

Both traditional QTL mapping and GWAS studies have been used to gain understanding of the genetic basis of resistance traits. The initial goal of these studies is often to find out basic information about the genetic underpinnings of resistance traits. Genetic mapping studies of this nature have taken place in both agricultural and natural systems, to different ends. Genetic mapping for defense traits has been particularly common in agricultural plants, where this information can be used in breeding. Often in agriculture, the trait of interest is resistance itself, rather than phytochemical or physical traits conferring resistance. Extent of feeding, insect weight gain, and/or insect mortality are common attributes used to infer resistance against multiple different herbivores and across a variety of crop species such as soybean and tomato (Rector et al. 2000; Komatsu et al. 2005; Yesudas et al. 2010; Vargas-Ortiz et al. 2018). Genetic mapping of resistance in natural systems,

Table 4.1 Positive and negative aspects of traditional QTL mapping analysis and genome-wide association mapping (GWAS)

Traditional QTL mapping		Genome-wide association mapping	
Pros	**Cons**	**Pros**	**Cons**
Relatively fewer genetic markers and genomic resources needed No statistical issues from population structure	Allelic variation is restricted to that of the wo parents in the initial cross Controlled crosses are not possible/feasible for many species QTL identified typically encompass larger genomic regions than GWAS	Encompasses allelic variation within and across natural populations Linkage blocks typically smaller than in QTL mapping, results in more fine-scale mapping	Relatively more genetic markers and genomic resources needed for adequate coverage Population structure can lead to false positives

Both techniques require very large sample sizes. These techniques can also be used together to identify candidate genes. Both methods can be used in population and/or functional genomics studies

while having some application to applied agricultural systems (Kloth et al. 2012), are most frequently done as part of fundamental evolutionary biology research, as part of the pursuit of understanding of the genetic basis of adaptation in natural plant populations (Orr and Coyne 1992; Rockman 2012).

4.6.2 QTL for Herbivory Resistance

Data accumulated from several decades of traditional QTL mapping and GWAS studies show that most resistance traits are quantitative traits that have multiple genes of both major and minor effects underlying phenotypes; as quantitative traits they may also be influenced by the environment. Model plant systems have had a head start in genetic mapping experiments due to the relative ease of obtaining genomic information and developing the genetic markers necessary for mapping. In the model system *Arabidopsis thaliana*, the first plant species to have a sequenced genome, informative work with QTL mapping of phytochemical defenses was developed two decades ago (Chan et al. 2010, 2011). These studies have contributed substantially to our understanding of the genetic underpinnings of resistance.

For example, an early study using genetic mapping in *A. thaliana* to investigate the genetic architecture of secondary compounds demonstrated that a relatively small number of genetic regions can underlie considerable variation in phytochemical resistance profiles. Glucosinolates are a large group of secondary metabolites in *Arabidopsis thaliana*, with an estimated 7–14 glucosinolates occurring in foliar tissue of a particular plant (Kliebenstein et al. 2001a). This allows *Arabidopsis* to generate a large number of possible combinations of glucosinolates in individual plants. In a study of the genetic basis of production of 34 different glucosinolates in *Arabidopsis* foliar tissue or seeds, variation at only five QTL resulted in 14 different foliar glucosinolate combinations (Kliebenstein et al. 2001a). Further work showed that a single QTL has a major effect in explaining variation in concentrations of a particular class of glucosinolates (Kliebenstein et al. 2001b).

Early genetic mapping studies exploring the overlap between genetic regions underlying resistance traits and those affecting herbivore performance also used *A. thaliana*. An investigation of QTL influencing feeding rates of generalist (cabbage looper, *Trichoplusia ni*) and specialist (diamondback moth, *Plutella xylostella*) herbivores demonstrated that five QTL for generalist insect feeding overlapped with those for glucosinolate resistance traits, while a relationship between loci underlying specialist herbivore feeding performance and glucosinolates was not found (Kliebenstein et al. 2002a). The diamondback moth can detoxify glucosinolates (Ratzka et al. 2002), potentially explaining the latter result. Similar results showing overlap between QTL underlying glucosinolate profile and those affecting *T. ni* performance were found in the Arabidopsis relative, *Boechera stricta* (Schranz et al. 2009).

While many specialists can detoxify or otherwise avoid the most detrimental effect of secondary compounds, their performance is frequently negatively affected by physical resistance traits such as trichomes (Rotter et al. 2018). Trichome density in *Arabidopsis* does influence oviposition success of the diamondback moth (Handley et al. 2005), and also provides resistance against herbivory by this

specialist (Sletvold et al. 2010). In a field experiment, both glucosinolates and trichomes reduced levels of generalist and specialist herbivore damage (Mauricio and Rausher 1997; Mauricio 1998). Subsequently, a single gene was identified that influences both trichome density and resistance to chewing insects in a field environment (Sato et al. 2019a).

4.6.3 Linking Genes to Herbivore Communities

Research linking QTL to resistance traits and to insect performance has most frequently been done in cruciferous herbaceous plants. In contrast, investigations of overlap between QTL underlying resistance traits and QTL influencing herbivore community composition has most often been done in woody systems.

In European aspen (*Populus tremula*), geographic variation exists for multiple genes involved in defense against herbivory (Bernhardsson and Ingvarsson 2012; Bernhardsson et al. 2013). Several of these genes show evidence of undergoing *selective sweeps* (Bernhardsson and Ingvarsson 2011), in which beneficial mutations rise so rapidly in frequency in a population due to natural selection that alleles in nearby linked regions are "swept" along. In a GWAS study, multiple single nucleotide polymorphisms (SNPs) were identified that were directly associated with herbivore community metrics such as species abundances for specialist herbivores, species richness for generalist herbivores, and species abundances within the galling, mining, and leaf rolling feeding guilds (Bernhardsson et al. 2013). A GWAS study in a North American aspen species, quaking aspen (*Populus tremuloides*) similarly found multiple SNPs underlying aspects of insect community composition (Barker et al. 2019b). This study also found overlap between SNPs associated with variation in insect communities and those associated with variation in multiple plant traits, demonstrating a mechanistic link for the gene-insect associations. Plant traits included the phytochemical resistance traits phenolic glycosides and condensed tannins (Barker et al. 2019b). A previous QTL mapping study in hybrid *Populus* (*P. trichocarpa* x *P. deltoides*) also indicates a potential role for phenolic glycosides and condensed tannins in influencing herbivore community composition (DeWoody et al. 2013). In hybrid aspen, QTL underlying variation in different feeding guilds of herbivores contain genes in the shikimate-phenylpropanoid pathway, which produces phenolic glycosides and condensed tannins (DeWoody et al. 2013).

4.7 Use of Genetics to Test Evolutionary Ecology Hypotheses

Techniques such as QTL mapping that identify genes or regions of the genome that underlie resistance traits can be used to test evolutionary hypotheses at previously unprecedented mechanistic levels. Isolating the effects of single genes or genetic regions on a phenotype and/or on herbivores can be done through the use of traditional breeding designs (e.g., Lowry et al. 2019) or gene silencing (e.g., Kessler et al. 2004).

4.7.1 Inferring Ecological Consequences from Genetic Data

Experiments designed to link genetics with ecology and/or evolution became more common in the early twenty-first century with the advent of the field of *ecological genomics* and a growing realization of the lack of ecological context for model organisms in laboratory environments. The primary goal of ecological genomics is to identify the genetic and molecular mechanisms underlying natural trait variation and influencing organismal response to the environment (Feder and Mitchell-Olds 2003; McKay and Stinchcombe 2008; Ungerer et al. 2008). Genetic or genomic information provides a connection between ecology and phenotypic-based studies to the evolutionary trajectory of defenses and populations. Ecological genetics approaches can be used to elucidate the functional and ecological consequences of genes, with breadth ranging from looking at trade-offs influenced by individual QTL or transcriptome studies of patterns of gene expression.

While some studies of natural selection on defense traits were done in natural environments, most previous work related to resistance was done with a small number of herbivores in a laboratory environment. One early example of the gains in knowledge obtained from moving from a lab to an ecological context occurred in *Nicotiana attenuata* (wild tobacco), which has become a model system for the study of signaling pathways involved in induced resistance (Baldwin 1998a, b; Xu et al. 2018). Three genes playing a major role in plant wound recognition and signaling response were silenced, thus dampening induced response to herbivory (Kessler et al. 2004). In the lab, plants with these genes silenced were more susceptible to herbivory by the specialist tobacco hornworm, *Manduca sexta*. In the field, the community composition of the herbivores attacking the plants was highly altered, with some novel herbivores showing a preference for the plants, imposing heavy damage, and ovipositing (Kessler et al. 2004). This demonstrates that host plant selection is not determined only by the constitutive defenses of a plant, but also by a plant's induced response to herbivory. This unique result would have been difficult to discover without investigation of the effects of this genetic manipulation in a natural environment.

4.7.2 Genetic Correlations and QTL-Level Trade-Offs

QTL-level studies can be used to test predictions of trade-offs between multiple aspects of defense, the framework for which was developed based upon phenotypic information. Questions within this realm include whether genes for different aspects of defense, or genes influencing resistance vs. traits related to life history strategy, co-localize. For example, are functional trade-offs that are predicted by plant defense hypotheses such as the Resource Allocation Hypothesis and Optimal Defense Theory based upon *genetic correlations* and/or *co-localization* at the genomic level? The presence of genetic correlations implies that the genes that underlie the traits are inherited together (Lande 1979; Via and Hawthorne 2002). Genetic correlations can be due to *pleiotropy*, when one gene influences multiple

traits, or to *linkage disequilibrium*, nonrandom associations of alleles at different genes affecting two traits (Falconer and Mackay 1996). Linkage disequilibrium is most often due to close physical linkage of the genes that underlie the traits (Lynch and Walsh 1998). Traditionally, genetic correlations have been estimated by assessing phenotypes of related individuals, and thus have not always been practical in studies of plant defense in non-model species. More recently, statistical methods have been developed for human data that allow genetic correlations to be calculated in very large groups of unrelated individuals based on genomic data (Lee et al. 2012; Sodini et al. 2018), although these methods are not often used in studies of plants. QTL mapping experiments, where QTL for multiple traits *co-localize*, or map to the same region of the genome, generally cannot distinguish whether the underlying mechanism for co-localization is pleiotrophy or physical linkage without being followed up by fine-mapping.

Knowledge of the extent of genetic correlations between traits can be more informative in studies of evolution than are phenotypic correlations. Analogous to studies of the evolution or evolutionary potential of a single trait, whereby genetic variation for a trait is necessary for evolution of the trait to occur within a population, genetic correlations are based upon genetic variance and covariances between traits and the rate and direction of their evolution depends on these parameters (Lynch and Walsh 1998). While phenotypic and genetic correlations sometimes correspond (Roff 1996), in many cases they do not (Willis et al. 1991), thus phenotypic correlations are not necessarily reliable substitutions when making evolutionary inferences for traits.

With genetic correlations, response to selection on one trait (i.e., changes in allele frequencies) will result in changes in other traits that are influenced by the same gene/group of genes. Such correlations can facilitate or constrain adaptation (Lande 1979; Via and Hawthorne 2005). QTL studies have been very informative in the exploration of the evolution of trade-offs in multiple aspects of defense, including between constitutive and induced resistance, between resistance and abiotic stress tolerance, and between resistance and other life history traits. Characterization of the strength and direction of genetic correlations between traits and/or the amount of phenotypic variation explained by QTL that co-localize and underlie traits allows inference about the evolutionary trajectory of these traits within populations (Conner and Hartl 2004).

Trade-offs between constitutive and induced defense are predicted to occur by Optimal Defense Theory, based upon allocation of resources given the probability of herbivory. Plant populations that experience consistent herbivory might invest more in constitutive defense, while populations that incur more sporadic herbivory might invest in induced defense only when necessary (Harvell 1990; Adler and Karban 1994; Cipollini et al. 2003). These patterns have been often, but not always, supported by phenotypic correlations (Karban and Baldwin 1997; Agrawal 1998). Investigation of genetic correlations and whether genetic underpinnings of these traits co-localize can help us to answer fundamental evolutionary questions regarding the genetic architecture of complex traits, and how trade-offs evolve.

Several studies of the genetic architecture of constitutive and induced defense have found QTL underlying these traits to co-localize. Kliebenstein et al. (2002b) found co-localization of QTLs influencing constitutive and induced glucosinolate levels in *Arabidopsis thaliana.* In contrast to the predictions of ODT, however, the genetic correlations between constitutive and induced defenses were positive. As predicted by ODT, negative genetic correlations were found between constitutive and induced trichome density in monkeyflower (*Mimulus guttatus*), with co-localization of some of the QTL underlying these traits (Holeski et al. 2010).

Trade-offs between resistance traits and abiotic stress tolerance have also been found to have a genetic basis. In a study of the mechanisms aiding or hindering range expansion in the ecological model species *Boechera stricta*, negative genetic correlations and co-localizing QTL were detected between glucosinolate production and drought stress tolerance. At the low elevation range boundary for the species, both increased levels of glucosinolates and increased drought stress tolerance were favored by selection. Thus, the genetic-based trade-off between these two attributes could contribute to limiting the range of the species by not allowing for simultaneous increase in resistance and increase in drought stress tolerance (Siemens et al. 2009; Olsen et al. 2019).

In monkeyflower, several studies have identified genetic-based trade-offs between resistance traits and traits related to life history strategy. In some perennial plants of *Mimulus guttatus*, an inverted portion of a chromosome (*DIV1*) underlies increases in both phytochemical resistance traits and traits related to long-term growth strategy such as plant height, adventitious root production, and number of stolons. The annual orientation of this region is associated with rapid development to reproduction and reduced phytochemical defense (Lowry et al. 2019). Similar trade-offs between rapid development to reproductive maturity and allocation to phytochemical defense is found within annual monkeyflower plants (*Mimulus guttatus)*. A QTL of relatively large effect underlies a trade-off between phytochemical resistance and developmental rate; plants that have more rapid time to reproductive maturity have lower levels of phytochemical defense than plants with slower development times (Kooyers et al. 2020).

4.8 Gene Expression and Herbivore Resistance

Advances in genomic technology have allowed greater understanding of how plants respond to herbivory at the genomic level. While this work is still biased towards a relatively small number of model and agricultural species (▣ Table 4.2), research in species that are closely related to model species have been able to coopt genetic tools and molecular genetic resources. Species in the Brassicaceae family such as *Boechera* and *Brassica*, for example, are often used for study of the genetics of plant-herbivore interactions, and this is largely possible due to the use of genetic resources developed in *Arabidopsis* (Mitchell-Olds 2001; Anderson and Mitchell-Olds 2011). Likewise, experimental use of plants in the *Solanum* genus has taken advantage of the genomic tools developed in tomato and potato relatives (Schmidt

Table 4.2 Genera used in genetic studies of plant resistance

Plant genus	Genome size of representative sequenced species	Year genome sequence made publicly available for a species in the genus
Arabidopsis	135 Mb	2000
Boechera	227 Mb	2017
Brassica	584 Mb	2011
Eucalyptus	640 Mb	2014
Glycine	1.1 Gb	2008
Ipomoea	750 Mb	2016
Mimulus	430 Mb	2008
Nicotiana	2.6–4.5 Gb	2012
Oryza	430 Mb	2002
Populus	500 Mb	2006
Solanum	840 Mb	2011
Triticum	17 Gb	2018
Zea (corn)	2.4 Gb	2009

This list represents many genera commonly used but is not comprehensive

et al. 2004). While a great deal of the work in gene expression has taken place in a greenhouse or laboratory environment, in the past decade multiple studies examining gene expression in plants grown in field-based common gardens have been published. These latter experiments have provided insight into the relationship between gene expression, ecologically-realistic abiotic and biotic environmental conditions, and population-level processes.

4.8.1 Transcriptome Profiling

Numerous studies have investigated patterns of gene induction and transcriptome patterns during and/or after herbivore feeding, along with the ecological effects of the induced changes in resistance. Expression profiling, also called *transcription profiling*, tracks the expression of hundreds to thousands of genes on *DNA microarrays*, whereby specific sequences are attached to a surface of a DNA chip, and act as probes to detect gene expression in samples (Bumgarner 2013). The expression profiles can then be compared in plants replicated across different environmental conditions of interest. In plant-herbivore interactions, this method has been used to compare gene expression in response to herbivores from different

feeding guilds (Broekgaarden et al. 2010), generalist versus specialist herbivores (Reymond et al. 2004), and plant response to different natural herbivore communities (Broekgaarden et al. 2010). Plant response to herbivores of different genotypes has even been assessed (Zytynska et al. 2016). Transcription profiling has been conducted in a number of species, including *Arabidopsis* and relatives, sorghum (*Sorghum bicolor*), tobacco (*Nicotiana attenuate*), rice (*Oryza spp.*), and tomato (*Lycopersicon esculentum*); this profiling has highlighted the complexity of plant response to damage and has provided insight into damage-induced signaling pathways. Large-scale differences in results across studies have also demonstrated the need for use of more standardized experimental designs (Thompson and Goggin 2006). Unless genes previously characterized in function have been identified and are used, gene expression profiling represents a whole plant response to herbivory and thus can include changes in expression in genes underlying direct defenses, indirect defenses, and a myriad of physiological changes.

4.8.2 Gene Expression Following Herbivore Activity

Transcription profiling has been used to investigate gene expression in response to mechanical versus specialist herbivore (*Pieres rapae*) damage (Reymond et al. 2000) and damage by generalist (*Spodoptera littoralis*) versus specialist (*P. rapae*) chewing herbivores in *Arabidopsis thaliana* (Reymond et al. 2004). While gene expression was quite different between plants with mechanical vs. specialist damage (Reymond et al. 2000), substantial overlap occurred between genes expressed in response to the generalist and specialist caterpillars (Reymond et al. 2004). Another study comparing gene expression in response to two generalist and a specialist chewing herbivore in tobacco (*Nicotiana attenuata*) found that the most overlap occurred between the two generalists (*Heliothis virescens* and *Spodoptera exigua*), although over 60% of the genes up- or down-regulated by the specialist (*Manduca sexta*) were similarly expressed following herbivory by the generalists (Voelckel and Baldwin 2004).

Studies of gene expression have been used to address evolutionary ecological hypotheses regarding induction of plant defenses by generalist versus specialist herbivores. For example, a long-standing paradigm in plant-herbivore interactions predicts that phytochemical plant defenses will have less of an effect on specialist herbivores than on generalists, and that when damaged by generalists versus specialist herbivores, plant responses will differ (Ali and Agrawal 2012). In the latter point, plant responses are both dictated by the plant and manipulated by the herbivore (Felton and Eichenseer 1999; Felton and Tumlinson 2008; Erb et al. 2012). Phenotypic evidence for differential plant response to generalists versus specialist is not consistent (Bowers and Stamp 1993; Agrawal 2000; Ali and Agrawal 2012), while evidence for differential plant response to feeding by herbivores of different feeding guilds is clearer (Ali and Agrawal 2012).

Patterns of gene expression have generally supported trait-based results in tests of this paradigm, showing that feeding guild may have a stronger effect on overall

differences in gene expression than does the diet breadth or degree of specialization of the herbivore. Analyses of gene expression following feeding by different feeding guilds in *Arabidopsis* showed limited overlap in the transcriptional response to feeding by chewing, cell-content feeding, and phloem-feeding herbivores (the caterpillar *Pieris rapae*, thrip *Frankliniella occidentalis*, and aphid *Myzus persicae*, respectively; De Vos et al. 2005). Broekgaarden et al. (2011) show similar results from a study of specialist caterpillars (*P. rapae*) and aphids (*Brevicoryne brassicae*) feeding on wild black mustard (*Brassica nigra*). Finally, in a study of four chewing lepidopteran herbivores and two aphid species, with generalists and specialists within each feeding guild, the effects of insect taxon or feeding guild had a substantially larger effect on patterns of gene expression than did insect diet breadth (Bidart-Bouzat and Kliebenstein 2011).

Gene expression data has highlighted at least some of the mechanistic basis for genotypic variation in resistance. In the *Arabidopsis* relative, white cabbage (*Brassica oleracea*), transcription responses to damage by a specialist (*Pieres rapae*) in two cultivars (genotypes) were compared using microarrays developed for *Arabidopsis* (Broekgaarden et al. 2007). The two genotypes differed in resistance as measured by *P. rapae* performance, although with this metric constitutive versus induced resistance cannot be disentangled. The two cultivars also differed fairly dramatically in transcriptional response, with 44% or more of the genes induced in one cultivar not induced in the other (Broekgaarden et al. 2007). Similarly, in a field experiment with 19 *Arabidopsis* accessions and ambient herbivory, more than half of the differences in gene expression in glucosinolate biosynthetic genes was among-accession variation (Sato et al. 2019b).

While much gene expression work has been done in a laboratory environment with one to three herbivores rather than in a natural context, some investigation of the relevance of transcriptional profiling in natural environments has been done. One such study elegantly ties herbivore community metrics to patterns of gene expression across plant genotypes. In a field study with two *Brassica oleracea* genotypes, nine herbivore species were present in similar abundances across the genotypes (Broekgaarden et al. 2010). Later in the season, one genotype hosted lower richness and abundances of both generalist and specialist herbivores than the other genotype. Levels of gene expression also differed more substantially between the genotypes relative to earlier in the season, with differences in expression levels in over 20 genes, including several genes known to play a role in herbivory defense (Broekgaarden et al. 2010).

When transcriptional profiling is used in combination with genes with a characterized function, a more comprehensive picture of plant response to herbivory can be obtained (He et al. 2020). Transcriptional profiling has been used for genes with previously characterized roles in direct and indirect defenses. In cucumber (*Cucumis sativus*), genes related to some direct defenses including phenylpropanoids and terpenoids were upregulated in response to spider mites (*Tetranychus urticae*), while genes underlying other direct defense phytochemicals were downregulated. Genes involved in the production of terpenoid emissions as an indirect defense were upregulated (He et al. 2020).

4.9 Genetic Basis of Indirect Defense

To date, study of the genetic basis of indirect defenses focuses almost exclusively on production of plant volatile compounds (Pearse et al. 2020). Levels, as well as the composition, of volatile blends emitted after herbivory are different than those emitted before herbivory; post-herbivory emissions of herbivory-induced plant volatiles (HIPVs) attract predators and parasitoids from multiple insect orders, as well as mites, nematodes, and birds (Dicke et al. 2003; McCormick et al. 2012). Plant volatiles can be induced by herbivore feeding and/or oviposition on a plant, and tend to attract primarily herbivore enemies (Kessler and Baldwin 2001, 2002; Poelman et al. 2008; Hilker and Meiners 2010), or egg parasitoids (Hilker et al. 2002; Hilker and Meiners 2002, 2006), accordingly.

Feeding by herbivores of different types and ages, feeding guilds, and abundances can affect the specific blend of volatiles that are released, and thus the enemies that are cued (McCormick et al. 2012). Volatiles induced by mechanical damage are different than those induced by herbivore feeding (Turlings et al. 1990; Baldwin et al. 2001). This could be a result of the differences in rate of tissue lost by herbivory vs. mechanical damage (Mithöfer et al. 2005), and/or to the lack of salivary cues by the herbivores (Turlings et al. 1990; Felton and Tumlinson 2008).

Research of indirect defenses has focused primarily on elucidating the signal-transduction pathways underlying plant response. This mechanistic research has taken place in model plant species, with genes underlying HIPV response identified in *Arabidopsis* (Van Poecke et al. 2001; Kappers et al. 2005), *Populus* (Irmisch et al. 2013; McCormick et al. 2019), tomato (Zhang et al. 2020), lima bean (Arimura et al. 2000), and maize (Erb et al. 2015), among others.

The genes underlying multiple aspects of direct and indirect defense have been identified in wild tobacco (*Nicotiana attenuata*; e.g., Dinh et al. 2013; Xu et al. 2020), and many aspects of the ecology of the species are known (Adam et al. 2018). However, extensions from the mechanistic genetic basis of HIPVs to plant fitness in natural environments to characterize the function of genes through generation of genetically altered plants are somewhat rare. One field-based study of HIPVs in wild tobacco estimated that they reduced the number of herbivores present by 90%, indicating the potential for substantial effects of HIPVs on plant fitness (Kessler and Baldwin 2001). Later studies have investigated the evolutionary and ecological effects of HIPVs in wild tobacco more directly through the use of genetically modified plants and have shown substantial effects of HIPVs on plant fitness.

One investigation of the effects of HIPVs on plant fitness in a field environment included plants that were genetically modified to have the genes underlying HIPVs silenced (Schuman et al. 2012). The specialist tobacco hornworm *Manduca sexta* had a large effect on flower production in the field environment; predation on Manduca was increased two-fold in plants that produced HIPVs, and these plants had twice as many buds and flowers as those in which HIPVs were silenced (Schuman et al. 2012). Another field experiment used wild tobacco plants that were genetically altered to produce reduced or enhanced levels of herbivore-induced volatiles, with some also having reduced levels of direct defenses (Schuman et al.

2015). Herbivore abundance was lowest on plants with enhanced levels of herbivore-induced volatiles, and these plants also had the lowest mortality rates. Enhanced levels of volatile production did not entirely compensate for reduced levels of direct defenses, in terms of plant mortality, but plants with enhanced levels of volatile emissions did improve the fitness of plants of other genotypes, when planted together (Schuman et al. 2015).

Work in wild tobacco using genetically modified plants has thus shown clear effects of variation in HIPV on plant fitness. Future studies investigating the effects of genetic variation in HIPV production within natural populations would provide more insight into the evolutionary potential of these indirect plant defenses.

Conclusions

Research in plant-herbivore interactions in the past half-century has shifted from a focus on phenotypic variation to an increasingly mechanistic genetic scale. We now know that genetic variation in resistance traits is widespread in natural populations. Characterizing patterns of genetic variation in traits and how natural selection by herbivores acts on these traits has given us a better understanding of evolutionary trajectories of resistance in natural populations.

Identification of genes or QTL underlying resistance traits has allowed us to test evolutionary and ecological hypotheses regarding the evolution of plant resistance at the level of individual genes or genetic regions, rather than at the level of phenotypes. Functional characterization of genes underlying herbivory resistance has led to a better understanding of the mechanistic pathways between genes and phenotypes.

As the variety of plant species in which genetic-based hypotheses can be tested increases, this will enable us to build a more comprehensive view of commonalities and differences in the genetic control of resistance. Investigations of gene expression and function across a broader array of species and in ecologically realistic environments will increase our understanding of how the genetic architecture of resistance functions and evolves in natural populations.

Key Points

Genetic and genomic studies of plant-herbivore interactions have contributed significantly to our understanding of:

- the genetic basis of plant resistance to herbivory
- evolutionary trajectories of resistance traits in natural populations
- evolutionary and ecological hypotheses for the evolution of resistance
- signaling pathways that underly plant response to herbivory

Question

We have extensive knowledge of the natural history of plant-herbivore interactions in some systems, based on a century or more of research. How can genetic work be used to complement natural history to inform our understanding of plant-herbivore interactions?

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Further Reading/Additional Resources

Anderson and Mitchell-Olds (2011) review ecological genomics and plant-herbivore interactions
A recent book chapter by Mijail De-la-Cruz, Sabina Velázquez-Márquez, and Juan Núñez-Farfán (2020) provides a complementary review of genomics work in plant-herbivore interactions
A book chapter by Heidel-Fischer et al. (2014) reviews plant transcriptomic responses to herbivory
A book chapter by Kliebenstein (2014) reviews quantitative genetic studies of plant resistance
Pearse et al. (2020) review the state of the field in the evolutionary ecology of indirect defenses