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REVIEW PAPER

Pivoting from *Arabidopsis* to wheat to understand how agricultural plants integrate responses to biotic stress

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Abstract

In this review, we argue for a research initiative on wheat's responses to biotic stress. One goal is to begin a conversation between the disparate communities of plant pathology and entomology. Another is to understand how responses to a variety of agents of biotic stress are integrated in an important crop. We propose gene-for-gene interactions as the focus of the research initiative. On the parasite's side is an *Avirulence* (*Avr*) gene that encodes one of the many effector proteins the parasite applies to the plant to assist with colonization. On the plant's side is a *Resistance* (*R*) gene that mediates a surveillance system that detects the Avr protein directly or indirectly and triggers effector-triggered plant immunity. Even though arthropods are responsible for a significant proportion of plant biotic stress, they have not been integrated into important models of plant immunity that come from plant pathology. A roadblock has been the absence of molecular evidence for arthropod *Avr* effectors. Thirty years after this evidence was discovered in a plant pathogen, there is now evidence for arthropods with the cloning of the Hessian fly's *vH13 Avr* gene. After reviewing the two models of plant immunity, we discuss how arthropods could be incorporated. We end by showing features that make wheat an interesting system for plant immunity, including 479 resistance genes known from agriculture that target viruses, bacteria, fungi, nematodes, insects, and mites. It is not likely that humans will be subsisting on *Arabidopsis* in the year 2050. It is time to start understanding how agricultural plants integrate responses to biotic stress.

Key words: *Avirulence* gene, effector-triggered susceptibility, effector-triggered immunity, gene-for-gene interactions, *Resistance* gene, *Susceptibility* gene, Triticeae.

Introduction

Complexities of plant–parasite interactions can be overwhelming. With the aid of allies, such as symbionts and pollinators, the plant grows and reproduces, all the while coping with abiotic stress and defending against phylogenetically diverse parasites. Parasites differ in how they attack, what they need from the plant, and their evolutionary potential for adaptation. What is a plant to do? As we learn more and more about the vast sensory and signalling abilities of plants (Farmer, 2014; Mescher and De Moraes, 2014), it becomes harder to understand how plants make sense of all this information and decide what to do.

Amongst all this complexity, a plant pathologist, Harold Flor, discovered something simple (Table 1). This is the gene-for-gene interaction between the plant and its parasite (Flor, 1946, 1955, 1971). We now know that the parasite's side of the interaction is an *Avirulence* (*Avr*) gene that encodes one of the many effector proteins the parasite applies to the plant to assist with colonization. The plant's side is a *Resistance* (*R*)

Table 1. *Gene-for-gene interactions between the plant* Resistance *gene and the parasite* Avirulence *gene*

Parasite genotype for *Avirulence* gene	**Plant genotype for *Resistance* gene**		
	R/R	***R/r***	***r/r***
Avr/Avr	Plant wins/Parasite loses	Plant wins/Parasite loses	Plant loses/Parasite wins
Avr/avr	Plant wins/Parasite loses	Plant wins/Parasite loses	Plant loses/Parasite wins
avr/avr	Plant loses/Parasite wins	Plant loses/Parasite wins	Plant loses/Parasite wins

gene that mediates a surveillance system, which detects the Avr protein directly or indirectly and triggers effector-triggered plant immunity. Mutations in the parasite's *Avr* gene allow the parasite to evade the *R* gene-mediated surveillance. Resistance in the plant and avirulence in the parasite are simply inherited as dominant traits, while susceptibility and virulence are recessive. *R* and *Avr* genes have significant impacts on the fitness of the plant and parasite, creating 'win/lose' situations (Table 1). Losing has major fitness consequences, ranging from partial to complete loss of fitness through death of the plant or parasite. The gene-for-gene concept has proved to be compelling for plant pathology, stimulating >70 years of research on an array of phylogenetically diverse microorganisms, including viruses, bacteria, fungi, oomycetes, and nematodes.

Because the gene-for-gene model does not entirely explain all interactions between plants and pathogens, plant pathology expanded on Flor's model (Chisholm *et al.*, 2006; Jones and Dangl, 2006; Dangl *et al.*, 2013). The expanded model places the 'adaptive' immune mechanism conferred by *R* gene surveillance alongside the 'basal' immune mechanism, which provides a contrast by detecting generic rather than specific features of pathogens. By showing relationships between mechanisms of plant immunity and parasite virulence, the expanded model raises questions about evolution and possibly co-evolution as well (Thompson and Burdon, 1992; Brown and Tellier, 2011). Plant and parasite molecules are important for the model, including plant proteins that function as receptors in basal and adaptive immunity, pathogen molecules that are detected by these receptors, and metabolites that contribute to plant susceptibility and immunity. Having a cloned *Avr* gene and its matching *R* gene facilitates testing the model.

Arthropods have not been incorporated into plant pathology's expanded model even though this would clearly benefit all parties, such as entomologists, plant pathologists, plant scientists, agricultural scientists, ecologists, and evolutionary biologists. We, and others, have argued for this incorporation in the hope that it will stimulate a conversation between entomologists and plant pathologists (Walling, 2000; Harris *et al.* 2003; Kaloshian, 2004; Kaloshian and Walling, 2005; Stuart *et al.*, 2012). Entomology and plant pathology bring different but complementary strengths to an integrated model of plant immunity, having taken very different paths during the past 50 years. Entomology embraced complexity by focusing on ecology, in particular chemical ecology (Howe and Jander, 2008), and has stressed interactions that occur in natural systems. Plant pathology embraced genetics starting with the discoveries of Flor (Agrios, 1997), and has devoted considerable effort to plant–pathogen interactions that occur in agriculture, sometimes also exploring the same interaction in nature (Thompson and Burdon, 1992). Plant pathology reaped the benefits of genomics much sooner, in part because plant pathogens are genetically simpler than arthropods but also because they are the kin of some of the first organisms that were sequenced, namely medically important pathogens. Entomology and plant pathology can learn a lot from each other.

The gene-for-gene interaction is one place where a conversation between entomologists and plant pathologists has already started. Many *R* genes targeted at insects have been mapped and a small number have been cloned. These include the *Bph* genes that provide protection against planthoppers (Du *et al.*, 2009). A planthopper gene that confers virulence to the *Bph1* gene has now been mapped and shown to exhibit the gene-for-gene relationship (Kobayashi *et al.*, 2014). The *Mi* gene has been cloned and provides protection against phylogenetically diverse parasites, namely whiteflies, aphids, and nematodes (Rossi *et al.*, 1998; Nombela *et al.*, 2003). One thing that has been missing from the conversation is the ability to compare *Avr* effectors of pathogens and arthropods.

This has changed with the recent cloning of the first arthropod *Avr* gene in the Hessian fly *Mayetiola destructor* Say (Aggarwal *et al.*, 2014). The discovery of this insect *Avr* gene comes 30 years after publication of the first cloned pathogen *Avr* gene (Staskawicz *et al.*, 1984). Since that first cloned pathogen *Avr* gene, many other *Avr* gene-encoded molecules have been identified for a range of plant–pathogen interactions that occur in natural and agricultural systems (Kamoun, 2006; Stergiopoulos and de Wit, 2009; Dangl *et al.*, 2013). Having a cloned arthropod *Avr* gene will allow the testing of plant pathology's expanded model for relevance to entomology. Also strengthening links between plant pathology and entomology is increasing evidence that insect-associated bacterial symbionts play an important role in plant–insect interactions (Frago *et al.*, 2012; Giron and Glevarec, 2014; Sugio *et al.*, 2014; Zhu *et al.*, 2014).

The second idea we discuss is a research initiative on integrated responses to biotic stress in wheat (*Triticum aestivum* L.). Wheat's importance for human civilization makes understanding its immunity a priority. A model for this initiative comes from the model plant *Arabidopsis thaliana* (L.) Heynh. We review the rich set of genetic resources that wheat has for the study of biotic stress, including 479 documented *R* genes targeted at viruses, bacteria, fungi, nematodes, insects, and mites. Agriculture relies on plant resistance to protect wheat

against its enemies. Moreover, wheat is not grown as a genetically modified (GM) crop and therefore relies on cisgenes rather than transgenes for protection. This contrasts with crops such as corn and soybean, which are protected against insects by transgenes from a bacterium, *Bacillus thuringiensis*. The incentive for these two crops to 'go GM' was, in large part, the promise of relief from biotic stress. Heretofore considered somewhat of a genetic nightmare because of its huge genome, wheat is becoming more tractable as a result of genome initiatives and an expanding molecular and genetic toolbox. This is an exciting time for the wheat community. A research initiative on biotic stress could be part of that excitement.

The gene-for-gene model

In the late 1930s and early 1940s, Flor used the flax rust [*Melampsora lini* (Ehrenb.) Lév.]–flax (*Linum usitatissimum* L.) interaction to do what would later be recognized as pioneering work in plant pathology (Flor, 1955, 1971; Loegering and Ellingboe, 1987). The model that resulted is the gene-for-gene model: for each gene conditioning a resistance reaction in the host plant, there is a corresponding gene in the parasite that conditions pathogenicity (Table 1). Flor's ideas developed during decades of what was undoubtedly tedious screening of flax genotypes for resistance to the fungal pathogen. He discovered that *M. lini* populations varied in their response to flax lines having dominant resistance traits. Some rust populations exhibited high frequencies of avirulence (the inability to colonize a particular resistant flax genotype) while others had high frequencies of virulence (the ability to colonize the same resistant flax genotype). The inheritance of avirulence was shown to be dominant and specific to certain flax genotypes. Simultaneously, the inheritance of resistance in flax was shown to be dominant. Eventually it was discovered that the flax *R* gene showed a gene-for-gene correspondence with the *Avr* gene of *M. lini* (Flor, 1955).

Flor proposed a parasite locus at which there are two possible alleles, an 'avirulent' (*Avr*) allele and a 'virulent' allele (*avr*). For this particular parasite locus, the plant then has a matching locus for which there are two possible alleles, a 'resistant' (*R*) allele and a 'susceptible' allele (*r*). Plants having the 'resistant' allele can only be colonized by parasites lacking the 'avirulent' allele, namely diploid parasites (e.g. rusts; Table 1) having two copies of the 'virulent' allele and haploid parasites having a single copy. Parasites carrying virulent alleles have the advantage of being able to colonize a greater number of host genotypes. Plants carrying resistant alleles have the advantage of being able to defend against a larger number of parasites. What Flor developed was a genetic model; however, he was prescient in proposing a biochemical mechanism as well (Flor, 1971) in which the gene product of the *Avr* gene is recognized by the product of a single dominant *R* gene, resulting in activation of a defence response that harms the parasite and helps the plant.

The gene-for-gene model (Table 1) is straightforward, makes predictions about things that will happen in the future, and has stimulated scientific inquiry in many fields, including genetics, molecular biology, evolutionary biology, and functional genomics. One feature it lacks is being able to explain all plant–parasite interactions. As one example, according to the gene-for-gene model, each *R* gene is specific to one species or race of pathogen. However, some *R* genes are not this specific, an example being the *Mi* gene, which confers resistance to parasite species belonging to two different phyla, namely insects and nematodes (Rossi *et al.*, 1998; Nombela *et al.*, 2003). A second criticism pointed out that the gene-for-gene model is inductive, being based on a single set of observations of just one plant–parasite interaction (Frank, 1994; Agrawal and Lively, 2002). To a large degree, evidence that was subsequently gathered from other plant–parasite interactions was taken as confirmation of the gene-for-gene model without bothering to test other models. A final problem comes from the vagueness of the term *Resistance* gene (Bent and Mackey, 2007). While the parasite's 'avirulent' loci are relatively easy to distinguish, being defined by the presence of a matching 'resistance' locus in the plant, the term *Resistance* gene is used more loosely, describing simple genetic traits in plants that have a measurable negative effect on parasites. Not all of the genes that we call *R* genes have been demonstrated to have a matching *Avr* locus in a parasite. Moreover some are durable when used in agriculture while others are not. Durability of *R* genes is discussed later in this review, using the specific example of wheat *R* genes.

A final problem with the gene-for-gene model is summarized by a question. Why does the parasite have an *Avr* gene if it does harm to the parasite by limiting the number of hosts it can exploit? Hogenhout *et al.* (2009) discuss this question and show how the answer triggered a paradigm shift in plant pathology. In the gene-for-gene model, the product of the *Avr* gene was viewed as an elicitor of plant resistance. The problem here is that this is the function of the *Avr* gene for the plant rather than the parasite. What changes in plant pathology's expanded model is recognition of the function of the *Avr* gene for the parasite, which is the production of a secreted 'effector' that is applied to the plant to aid in colonization and exploitation of the plant's resources (Hogenhout *et al.*, 2009). Avirulence effectors presumably comprise a subset of the complete set of the parasite's effectors. This paradigm shift has been important for plant pathology, shifting focus from the plant, which gains our attention by being our ally in agriculture, to the pathogen, which we now fully acknowledge as a worthy adversary.

The expanded model

In contrast to the gene-for-gene model, which is interested in the genetic basis of plant resistance and parasite virulence, plant pathology's expanded model (Chisholm *et al.*, 2006; Jones and Dangl, 2006; Dangl *et al.*, 2013) presents two mechanisms of plant immunity and how parasites adapt to these two mechanisms. It is an expanded model in the sense that gene-for-gene resistance is one of the two immune systems and *Avr* gene loss of function is one of the ways that the parasite adapts. Because immunity is about having receptors that detect alien molecules, the model is also a biochemical model of what happens during the very first stages of attack. For many pathogens, this initial

attack occurs at the scale of an individual cell, typically an epidermal cell. This scale seems relevant for gall inducers, such as the Hessian fly, and for insects such as aphids and whiteflies whose needle-like mouthparts (stylets) find their way to feeding sites in the phloem by carefully moving between cells (Kaloshian and Walling, 2005). Plant pathology's expanded model is also interested in spatial aspects of attack and plant immunity. The apoplast comprises what lies outside the plasma membrane, including the plant surface, the cell wall, and spaces between cells. The symplast comprises what lies inside the plasma membrane, including everything found in the cell's cytoplasm and the cell's connections via plasmodesmata with the cytoplasm of the plant's other cells.

The plant's basal immune system is the first line of defence (Fig. 1). Plants have pattern recognition receptors (PRRs) involved in recognition of microbe/pathogen/damage/herbivore-associated molecular patterns (MAMPS/PAMPS/DAMPS/HAMPS). As well as telling the plant that the parasite has arrived, the basal immune system has the task of distinguishing between microbial friends and foes (Jones and Dangl, 2006; Chisholm *et al.*, 2006; Bent and Mackey, 2007). The parasite molecules that enable detection are typically broadly conserved, encoded by 'housekeeping' genes essential for functioning of the pathogen. Examples of PAMPs (pathogen-associated molecular patterns) are chitin, indicating attack by fungi, or flagellin, indicating attack by bacteria (Macho and Zipfel, 2014). Examples of DAMPs (damage-associated molecular patterns) are molecules associated with physical damage to the plant, for example, oligosaccharides derived from fragments of the cell wall and ATP (Cao *et al.*, 2014). Examples of HAMPs (herbivore-associated molecular patterns) are molecules found in insect saliva (Felton *et al.*, 2014). Detection results in the co-ordinated set of downstream defence responses that harm the parasite, a response to pathogens known as PAMP-triggered immunity (PTI). Erb *et al.* (2012) discuss the degree to which plant recognition of herbivore attack results from DAMPs versus HAMPs.

The parasite feature that addresses problems created by the plant's basal immunity is 'effector-triggered susceptibility' (Fig. 1). Effectors are defined as 'all pathogen proteins and small molecules that alter host-cell structure and function' (Hogenhout *et al.*, 2009). As pointed out by Kamoun (2006, 2007) and Hogenhout *et al.* (2009), parasite effectors are examples of Dawkins' (1999) 'extended phenotype'. Thus, while the gene encoding the effector is found in the genome of the pathogen, it produces its phenotype in a different organism, namely the host plant. Suppressing the plant's basal immunity was originally seen as the primary function of effectors. We now know that parasite effectors have many functions other than suppression of basal immunity (Dangl *et al.*, 2013; Lapin and Van den Ackerveken, 2013). The role parasite effectors play in inducing the plant's susceptibility genes is discussed later in the review.

The parasite's effector-based strategy is exploited by the plant's *R* gene-mediated surveillance system (Fig. 1). This is 'effector-triggered immunity' (ETI). Surveillance focuses on a specific effector encoded by a parasite *Avr* gene, with detection triggering a rapid downstream defence. Detection can result from either a direct interaction between the R product and Avr product (Dodds *et al.*, 2006) or an indirect interaction. In the latter case, the R product 'guards' a subcellular target of the parasite's Avr effector and, upon detecting a change in the target, triggers downstream responses (Dangl and McDowell, 2006). Evolutionary biologists are interested in possible constraints via fitness costs of *R* gene-mediated surveillance and downstream defence responses (Burdon and Thrall, 2003; Brown and Tellier, 2011).

Greater stealth is a parasite response to the plant's *R* gene-mediated surveillance system (Fig. 1). This can be achieved in at least two different ways. The parasite can evolve new effectors that suppress the immunity triggered by other effectors. Alternatively the parasite can modify the specific Avr effector that is under surveillance so that detection fails (Dangl *et al.*, 2013; Ashfield *et al.*, 2014). To achieve the latter, the modification that is needed depends on how the Avr product

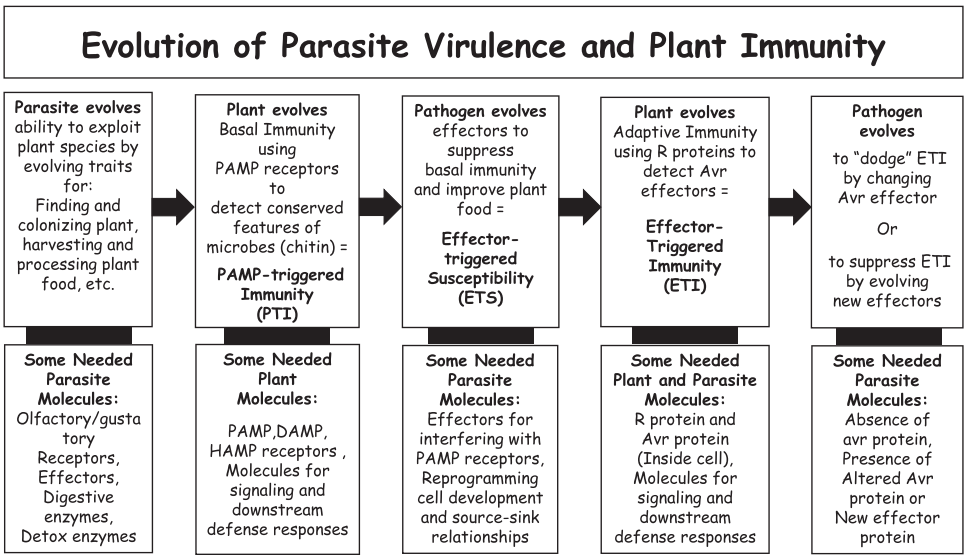

Fig. 1. Expanded model of parasite virulence and plant immunity based on ideas from plant pathology presented in Chisholm *et al.* (2006), Jones and Dangl (2006), and Dangl *et al.* (2013). (This figure is available in colour at *JXB* online.)

interacts with the R product. If there is a direct interaction between the R product and the Avr product, any mutation that prevents that direct interaction will suffice, including mutations that do not interfere with the functioning of the Avr effector for the parasite. If there is an indirect interaction, wherein the R product guards a subcellular target of the Avr effector, the mutation must prevent the Avr product from interacting with the target. Since such mutations can result in Avr loss of function for the parasite, evolutionary biologists are interested in fitness costs of virulence (Leach *et al.*, 2001; Brown and Tellier, 2011) and their relationships with durability of *R* genes in agriculture (Leach *et al.*, 2001). Major fitness costs of *Avr* loss of function may explain the decades-long durability of a number of widely deployed *R* genes in agriculture. This is relative to other *R* genes that have been quickly defeated, presumably because the parasite experienced little or no fitness cost for evolving virulence (Leach *et al.*, 2001; Bent and Mackey, 2007; Brown and Tellier, 2011).

Hessian fly–plant interactions

The Hessian fly (order Diptera: family Cecidomyiidae) is an economically important pest of major cereal crops, primarily bread wheat *T. aestivum* and pasta wheat *T. turgidum* L. ssp. *durum*, but also rye *Secale cereale* L., triticale (×*Triticosecale* Wittmack), and barley *Hordeum vulgare* L. Populations are present throughout the Mediterranean region as well as North Africa, Europe, Western and Central Asia (including China), North America, and New Zealand.

The host range of the Hessian fly is surprisingly broad. Most gall inducers are specialists, attacking just one or a small number of plant species. Almost all herbivorous species belonging to the family Cecidomyiidae are specialists (Gagné, 1989, 2004). All of the Hessian fly's hosts are grasses. Most belong to the tribe Triticeae (17 different genera), there being a few host species in the closely related tribe Bromeae (Harris *et al.*, 2001). Host plants include all known progenitors of wheat, for example *Aegilops tauschii* and *T. turgidum*, as well as grasses that diverged from the wheat lineage millions of years ago, for example ~10–14 and 7 million years ago for barley and rye, respectively (Gill *et al.*, 2004). Phylogenetic relationships suggest ancient relationships with grasses (Gagné, 2004). Including the Hessian fly, there are 29 known *Mayetiola* species (Gagné, 2004). Hosts of the *Mayetiola* species exhibit a range of genetic distances from *T. aestivum*, the most distant being oat (tribe Aveneae), which is not a host of the Hessian fly. While little is known about the other 28 *Mayetiola* species, the Hessian fly appears to be different in having a broader host range that encompasses the narrower host ranges of its relatives, including the barley midge *Mayetiola hordei* (Gagné, 2004). Understanding the role that the Hessian fly's effectors play in host range may benefit from a number of well-studied bacterial gall inducers, including *Pantoea agglomerans*, a species that can expand its host range by acquiring new effectors (Barash and Manulis-Sasson, 2009), and *Agrobacterium tumefaciens*, a well known genetic model (Zupan *et al.*, 2000).

Studying the wheat–Hessian fly interaction benefits from its experimental tractability. Gene-for-gene interactions are associated with dramatic phenotypic differences that have dramatic fitness consequences for both the Hessian fly and the wheat plant, an example being the interaction between *H13*-mediated resistance and *vH13*-mediated virulence (Table 2). Plants can be screened as a 1- to 2 -leaf seedling. Insects can be held in cold storage for up to 1.5 years. Together these features facilitate rapid resistant screening of thousands of plants using relatively little labour and greenhouse space. The plant's susceptible response is apparent within 5 d and can be scored quickly without need of a microscope or measurement. The susceptible seedling typically stops growing. Its leaves turn a bluish green (Anderson and Harris, 2006, 2008). Plants lacking this response are dissected to make sure they were attacked by larvae and therefore are truly resistant rather than 'escapes'.

For the most part, scoring differences between avirulent and virulent larvae is easy. Both are found in the same location at attack sites at the base of the plant. Avirulent larvae die in the neonate stage, which is small (0.45 mm long) and red in colour. Virulent larvae live and grow quickly, and conveniently change their colour from red to white. A complication arises when there is simultaneous attack by both avirulent and virulent larvae (Fig. 2), a phenomenon known as obviation (Baluch *et al.*, 2012). In the example of larvae attacking *H13* wheat, *H13* avirulent larvae die when they alone attack the plant. *H13* virulent larvae live. However, *H13* avirulent larvae can also survive if they attack the *H13* plant alongside virulent larvae. This suggests that induced susceptibility trumps induced resistance (Baluch *et al.*, 2012). During screening, complications due to obviation are avoided by using a strain of Hessian fly that is uniformly avirulent.

In contrast to plant pathogens, the Hessian fly has behavioural traits that make important contributions to interactions with plants. The behavioural repertoire and sensory

Table 2. *Phenotypic responses of wheat seedlings and Hessian fly neonate larvae associated with gene-for-gene interactions between the wheat* H13 Resistance *gene and Hessian fly* Avirulence *gene* vH13 *(Harris* et al.*, 2012)*

Hessian fly *Avirulence* gene *vH13*	**Wheat *Resistance* gene *H13***	
	H13	***h13***
$vH13^{A}$	Seedling plant lives/Neonate larva dies (no nutritive tissue)	Seedling plant dies/Neonate larva lives (nutritive tissue)
$vH13^{V}$	Seedling plant dies/Neonate larva lives (nutritive tissue)	Seedling plant dies/Neonate larva lives (nutritive tissue)

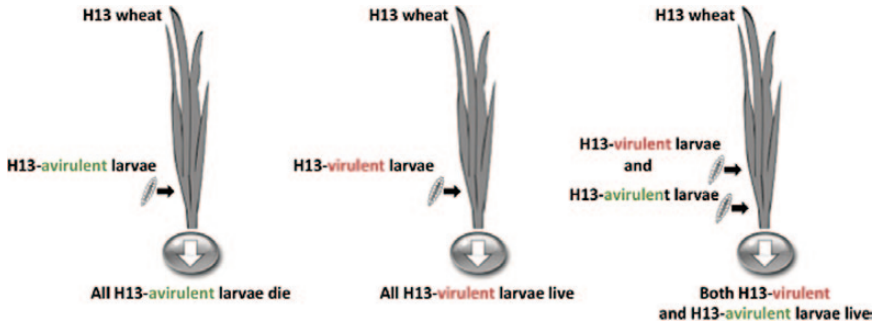

Fig. 2. The phenomenon of Hessian fly obviation, wherein induced susceptibility trumps induced resistance and, by doing so, allows survival of *H13* avirulent larvae on *H13* wheat. (This figure is available in colour at *JXB* online.)

capabilities of the adult female are surprisingly sophisticated given its small size and an adult lifespan of just 1 d (Harris *et al.*, 2003; Andersson *et al.*, 2014). We know of at least one flaw in the Hessian fly's host selection behaviour. Host preference behaviour of the ovipositing adult female is expected to correspond to the performance of her offspring. Thus the female should choose plant species and genotypes that are best for offspring survival, growth, and reproduction (Schoonhoven *et al.*, 2006). However, this is not the case for the Hessian fly and *H* genes. Plants with or without *H* genes receive similar numbers of eggs (Harris *et al.*, 2001). Why doesn't the Hessian fly evolve mechanisms that allow detection of *H* genes that can cause 100% mortality of offspring? The Hessian fly's inability to evolve these mechanisms makes more sense when one realizes that, in order to have optimal egg-laying behaviour regarding *H* genes, the female would need to know which *H* gene the plant has, as well as the virulence of her own offspring relative to that particular *H* gene (Harris *et al.*, 2001).

The female typically places eggs on the adaxial surface of the blade of the seedling's youngest leaf, a behaviour that presumably helps neonate larvae find the 'reactive sites' that are amenable to formation of the nutritive tissue (Ganehiarachchi *et al.*, 2013). The larva emerges from the egg 3 d later. It is incapable of moving to another plant if the female has chosen a plant that is not suitable. The larva slowly crawls down the leaf blade (1 cm min^{-1}), eventually entering the shelter offered by the bundled leaf sheaths. It moves down the sheath until it reaches a zone within 0–2 cm of the leaf base, where it uses its tiny mandibles, which are connected to the salivary glands, to attack epidermal cells on the abaxial surface of a younger leaf that is adjacent to the leaf that received eggs (Hatchett *et al.*, 1990; Harris *et al.*, 2006, 2010). Several days later after first arriving at the feeding site, the larva moults to the second instar. It now has lost the creeping pads it used to migrate to attack sites. Feeding as a sessile organism after a brief mobile phase makes the Hessian fly similar to whiteflies, which also appear to have gene-for-gene interactions (Kaloshian and Walling, 2005).

Two days after the initial attack, gall nutritive cells appear in the epidermis and mesophyll (Harris *et al.*, 2006). This is the gall nutritive tissue. The enriched cytoplasm of nutritive cells has been described for many insect gall inducers (Bronner, 1992; Rohfritsch, 1992). Soon after the nutritive cells first appear, they begin to self-destruct (Harris *et al.*, 2006). Holes appear in cell walls and the cytoplasm breaks down and is released to the leaf surface. This is where the first-instar larva sits sucking up fluids (Refai *et al.*, 1956). There is a clear association between plant growth deficits and the induced nutritive tissue (Table 2; Harris *et al.*, 2012). This is common for gall inducers, which reprogramme source–sink relationships within the plant, the result being insect growth at the expense of plant growth (Larson and Whitham, 1991). In the case of the Hessian fly, plant growth effects do not appear to be density dependent. A single larva is sufficient to induce stunting of the plant (Berzonsky *et al.*, 2003; Harris *et al.*, 2012).

In spite of being a major focus of research for >50 years, the gall-inducing status of the Hessian fly was not discovered until recently (Harris *et al.*, 2006). The discovery was made possible by the skills of a French scientist, Dr Odette Rohfritsch, known for her imaging studies of subcellular features of gall nutritive cells (Rohfritsch, 1992). Prior to the discovery, scientists believed that the Hessian fly larva's growth effects on the plant (referred to as 'stunting') were the result of 'enzymatic substances' (Berzonsky *et al.*, 2003). In terms of phylogeny, it seems obvious that the Hessian fly would be a gall inducer. It is a member of the family Cecidomyiidae which, along with the wasp family Cynipidae, contains the preponderance of insect gall-inducing species (Gagné, 1989; Stone and Schönrogge, 2003). A misconception about cecidomyiid galls contributed to the delay in recognizing the Hessian fly as a gall inducer. Not all galls have a macroscopic plant growth that surrounds or encloses the gall inducer and its nutritive tissue (Bronner, 1992; Rohfritsch, 1992; Stone and Schönrogge, 2003). However, all galls do have some type of microscopic nutritive tissue. Because its gall lacks a macroscopic gall tissue and can only be seen microscopically, the Hessian fly was not seen as a gall inducer.

The discovery that the Hessian fly is a gall maker has changed many things. First and foremost, it brought recognition of the equal importance of induced resistance and induced susceptibility (Harris *et al.*, 2012). The paradigm shift has inspired the characterization of the plant's state of induced susceptibility, including changes in plant growth (Anderson and Harris, 2006, 2008), alterations of nutrients and host metabolic pathways (Saltzman *et al.*, 2008; Zhu *et al.*, 2008), suppression of defence (Liu *et al.*, 2007), and increased permeability of the plant epidermis (Williams *et al.*,

2011). It also has created opportunities for comparisons with other plant parasites that induce galls, including cyst and root knot nematodes and many bacterial and fungal pathogens, including the gall inducer *Agrobacterium tumefaciens*.

Hessian fly and the gene-for-gene model

The discovery of the gene-for-gene relationship between wheat's *H* genes and the Hessian fly's *Avr* genes was undoubtedly influenced by Flor's landmark discoveries. The first record of wheat resistance to the Hessian fly came in 1782, just a few years after the arrival of the Hessian fly in North America (Fitch, 1847). Field observations and selection of resistant cultivars continued throughout the 19th century. The systematic search for resistance began in the late 19th century (Packard, 1880, 1928), and studies of the genetic basis of resistance began in the middle of the 20th century. For the first *H* genes, resistance turned out to be an independent, simply inherited, dominant trait. This is also the case for most of the 37 *H* genes that are now known (Berzonsky *et al.*, 2003). The next step was to test populations of Hessian fly against the *H* genes. Virulence to specific *H* genes was discovered and subsequently determined to segregate as an independent, simply inherited, recessive trait (Gallun and Hatchett, 1969; Hatchett and Gallun, 1970). Hessian fly virulence is at the greatest levels in the Fertile Crescent, the known centre of origin for wheat and the putative centre of origin of the Hessian fly (El Bouhssini *et al.*, 2009). In this region, there are two *H* genes, *H25* and *H26*, which provide 100% protection. Because virulence to the two *H* genes has also never been found in Hessian fly populations in the USA and North Africa, it appears that these two *H* genes confer broad-spectrum resistance. Virulence to the remaining 35 *H* genes varies across Hessian fly populations (Cambron *et al.*, 2010). Nevertheless many of the *H* genes are considered useful for agriculture because virulence frequency is low.

Hessian fly and the expanded model

For Hessian fly–wheat interactions, nothing is known about basal immunity (Fig. 1). A hint of defence mechanisms other than *H* gene-mediated resistance comes from susceptible wheat plants (Anderson and Harris, 2006, 2008). A majority of susceptible seedlings attacked by the Hessian fly die. Those that survive do so by initiating new growth from a meristem other than the apical meristem. If this new growth can be initiated, the surviving susceptible seedling has a surprising ability to make up for its initial delayed growth (Anderson *et al.*, 2011). It seems possible that compensatory growth responses, such as these, are enabled by a non-specific detection system mediated by DAMP or HAMP receptors that act as a surveillance system for protecting the apical meristem. Knowing when attack begins and when it ends provides the plant with the option of initially diverting resources away from the attacker and, after attack is completed, redeploying them for the purposes of compensatory growth (Orians *et al.*, 2011).

The second panel of the model (Fig. 1) shows the parasite using its effectors to suppress basal immunity and/or improve plant food. While the process leading to a full understanding of these molecules and mechanisms is well underway in plant pathology (Dangl *et al.*, 2013), it is only beginning for the Hessian fly. The cloning of the *vH13 Avr* gene, which is discussed in the following section, will begin the process of determining actual, rather than putative, function. We would like to know how *vH13* gets into the epidermal cell, where it goes, and what it does when it gets there. Creating genetically modified strains of Hessian fly, expressing or not expressing *vH13*, also would show what is gained by expressing *vH13*. As is the case for plant pathogens, functional redundancy among effectors, which is proposed for effectors of plant pathogens (Stergiopoulis and de Wit, 2009), may allow other effectors to replace *vH13* when it no longer functions. As discussed in the next section, the Hessian fly may have hundreds of effectors (Chen *et al.*, 2010). If this is the case, a full understanding of the Hessian fly's effector-triggered susceptibility will require considerable effort.

The third panel of the model (Fig. 1) shows the plant's adaptive immunity system mediated by *R* genes that detect specific *Avr* effectors. Here the Hessian fly research community is constrained by not having cloned *R* genes; for example, the *H13* gene that matches the cloned *vH13 Avr* gene, or the *H26* gene for which no virulence has been found worldwide. A cloned *H13* gene would facilitate a determination of whether the *H13* product interacts with the *vH13* product directly or indirectly. For plants attacked by the Hessian fly, it seems that a key function of *R* gene-mediated defence is protecting the seedling, which is frequently killed (Anderson and Harris, 2008). Older plants survive attack, although numbers and viability of offspring are reduced relative to non-attacked plants. Remarkably, protection of the seedling incurs no fitness cost for the plant (Anderson *et al.*, 2011). This absence of fitness costs raises the possibility that resistance results because the plant fails to respond to the Hessian fly's attempt to induce susceptibility. Thus, the plant fails to oblige. Several lines of evidence indicate that defence against the Hessian fly is an active response. For example, imaging studies show fortification of cell walls and enhanced secretory activity of epidermal and mesophyll cells (Harris *et al.*, 2010). Both responses have also been observed in plants exhibiting penetration resistance to fungi (An *et al.*, 2006; Hückelhoven, 2007). A number of biochemical changes are associated with gene-for-gene resistance to the Hessian fly, including the production of toxins (Subramanyam *et al.*, 2006, 2008), reactive oxygen species (Liu *et al.*, 2010), and materials for remodelling and strengthening the cell wall (Kosma *et al.*, 2010; Williams *et al.*, 2011; Zhu *et al.*, 2012; Khajuria *et al.*, 2013).

The fourth panel of the model (Fig. 1) shows the parasite avoiding the plant's ETI, either by changing its Avr effector or by evolving new effectors in order to suppress ETI. In the following section we discuss how the Hessian fly has been able to change one of its *Avr* effectors, *vH13*, and, by doing so, dodges ETI mediated by the *H13* resistance gene. Possibly there is a reproductive cost of evolving virulence: adults of virulent Hessian fly strains are smaller than adults

of an avirulent strain (H. Zhang *et al.*, 2011). In the Hessian fly, adult size is strongly correlated with fecundity of females and fertility of males (Bergh *et al.*, 1990). This is common for insect species that do not feed as adults and therefore emerge with their full complement of eggs or sperm.

Cloning of the first insect *Avirulence* gene

The search for Hessian fly effectors has proceeded along two paths. One has used bioinformatics to examine the transcriptomes of the neonate first-instar larva, which colonizes the plant. Studies of the salivary glands have revealed hundreds of unique Hessian fly transcripts encoding proteins carrying signal peptide sequences (Chen *et al.*, 2004, 2006, 2008, 2010). The structures of the secreted salivary gland proteins (SSGPs) encoded by these transcripts provide evidence that they are effectors, the proteins being relatively small and showing no sequence similarities to other known proteins. A measure of diversifying selection is seen among many of the putative effectors that belong to the gene families. In many of these families, there is greater similarity among family members within the coding regions of the genes than in the non-translated portions of the genes (Chen *et al.*, 2010).

Classical genetics is a complementary approach for discovery of parasite effectors. Features of wheat and Hessian fly have facilitated studies of the inheritance of *R* genes and matching *Avr* genes. Wheat is amenable to experimental crosses. In the absence of genetically modified wheat plants, a set of isogenic wheat lines, one a susceptible line without an *H* gene and the other eight lines expressing one of eight different *H* genes, has provided useful tools for dissecting gene-for-gene resistance in wheat (Patterson *et al.*, 1994; Xu *et al.*, 2011). The Hessian fly is a good genetic model, having a small genome, polytene (giant) chromosomes, a short generation time (1 month), adults that are amenable to experimental crosses, and the option of raising continuous generations. An additional option is cold storage of genetic strains.

To create structured mapping populations for the Hessian fly (Fig. 3), crosses are made between sister females, which are homozygous virulent or avirulent to the resistance gene in question, and a single male, which is either homozygous or hemizygous for the alternative condition. Because the female Hessian fly usually produces offspring of only one sex (unisexual progeny, a feature of cecidomyiid flies), it is important that at least one of the sister females produces F_1 females while another produces F_1 males so that these F_1 females and males can be intermated to produce an F_2 generation. This is not a significant difficulty in the Hessian fly because female-producing females and male-producing females segregate in populations in a 1:1 ratio (Benatti *et al.*, 2010). The F_1 and all subsequent generations are reared and maintained on susceptible wheat seedlings. For the F_2 and all subsequent generations, the population is sampled for genotypes, first by creating test crosses with homozygous virulent individuals and then by scoring the insect and plant phenotypes that result when resistant plants are attacked by offspring of the test cross. The precision with which genetic mapping proceeds

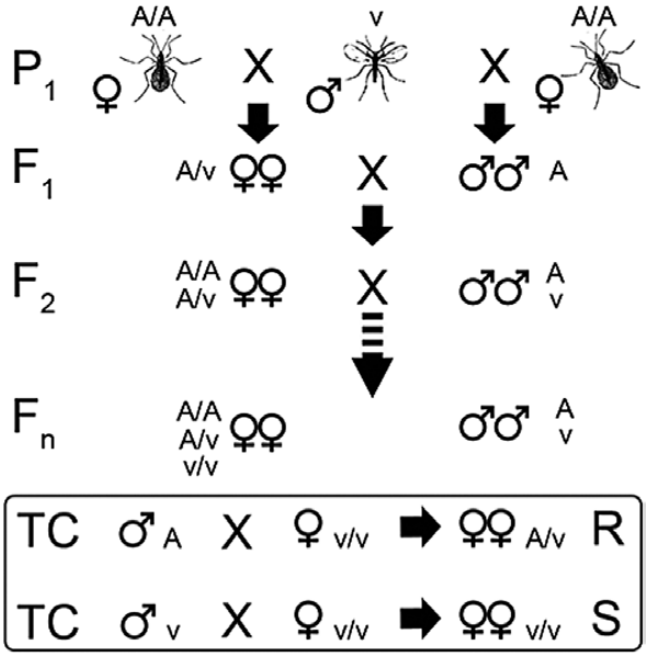

Fig. 3. Experimental crosses of Hessian fly that were used to create structured mapping populations.

depends on the expression and penetrance of resistance, which differ among *H* resistance genes and cultivars carrying the *H* gene. This means that mapping virulence has been easier for 'reliable' *H* genes such as *H13*.

The first genetic investigations showed that Hessian fly virulence in wheat segregated as independent, simply inherited, recessive traits in populations (Gallun and Hatchett, 1969; Hatchett and Gallun, 1970; Gallun, 1977). With the advent of molecular markers, *Avr* genes corresponding to seven *H* resistance genes in wheat (*H3*, *H5*, *H6*, *H9*, *H13*, *H24*, and *Hdic*) were assigned to Hessian fly chromosomes with improving resolution over a 10 year period (Rider *et al.*, 2002; Behura *et al.*, 2004; Lobo *et al.*, 2006; Stuart *et al.*, 2008, 2012).

The construction of a Hessian fly FPC-based physical map with end-sequenced bacterial artificial chromosome (BAC) contigs (Aggarwal *et al.*, 2009), in conjunction with association mapping, finally made it possible to identify three different mutations (transposon insertions) conferring virulence to a single wheat *R* gene, *H13* (Aggarwal *et al.*, 2014). The three *Avr* mutations, which appear to have evolved independently, disrupt an *Avr* gene (*vH13*) that encodes a small modular protein with an N-terminal signal peptide. Mutations that confer virulence by preventing *Avr* gene transcription are suggestive of indirect rather than direct R product–Avr product interactions (Stergiopoulous and de Wit, 2009). The *vH13* gene is transcribed in the salivary glands of first-instar *H13*-avirulent larvae, but is not transcribed in *H13*-virulent larvae. It was not identified in previous salivary gland transcriptome analyses (Chen *et al.*, 2008), confirming that the current inventory of Hessian fly putative effectors expressed in first-instar larvae is incomplete. Three different *vH13* avirulence alleles exist in Hessian fly populations. These differ with respect to the number of imperfect amino acid repeats present in the

protein. The existence of these alleles suggests that *vH13* is experiencing diversifying selection for functional adaptation. This also appears to be the case for other putative Hessian fly effectors, whose non-coding segments are more similar than the segments that encode mature proteins (Chen *et al.*, 2010). Functional assays are being developed to determine how *vH13* functions for the Hessian fly in effector-triggered susceptibility and how it functions for the wheat plant in ETI.

Discovery of Hessian fly virulence to *H* genes led to an effort, starting in the 1970s, to 'biotype' Hessian fly populations prior to making a decision about which *H* gene should be deployed in regional wheat cultivars (Berzonsky *et al.*, 2003). In order to determine the frequency of 'biotypes' within a population, scientists scored the virulence of the offspring of a large number of females (>100) in relation to four wheat 'differentials', each carrying a different commonly deployed *H* gene. An interesting discovery revealed by 'biotyping' was the presence of significant frequencies of virulence in populations that have never knowingly been under selection pressure from the *H* gene (e.g. Cambron *et al.*, 2010).

'Biotyping' a Hessian fly population is time-consuming, laborious, and imprecise. It is now being replaced by genetic screening (Stuart *et al.*, 2012). A 'biotype' is, in fact, a simple genotype distinguished by mutations in single genes that segregate in populations. Thus, it is more appropriate and informative to speak of the frequency at which virulence and avirulence alleles are segregating at *Avr* loci in populations (Stuart *et al.*, 2012). Likewise, selection for virulence simply favours the selection of virulence alleles at specific *Avr* loci and is predicted to have little to no effect on the rest of the genome. For genetic screening, sampling of Hessian fly populations has been facilitated by the discovery and synthesis of a female-produced sex pheromone (Andersson *et al.*, 2009). The pheromone is highly attractive to adult males, which are caught in pheromone-baited traps (Anderson *et al.*, 2012) and whose DNA can be assayed (Stuart *et al.*, 2012; Chen *et al.*, 2014*a*).

Silencing susceptibility: a second path to plant resistance

Some plant parasites change the host plant prior to colonization. This is done to create a better environment for the parasite's survival, growth, and/or reproduction. We typically do not know the exact parameters of that environment. However, it is clear that the parasite's manipulation of susceptibility genes plays a role in creating the beneficial environment (Oliver *et al.*, 2012; Hückelhoven *et al.*, 2013; Lapin and Van den Acherveken, 2013). Susceptibility genes are defined as 'host genes reprogrammed by pathogens that are required for pathogen survival and proliferation' (Dangl *et al.* 2013). In the case of plant resistance to pathogens, both recessive and dominant *R* gene-mediated resistance have been defeated by the induction of a susceptibility gene (Yang *et al.*, 2006; Antony *et al.*, 2010).

Silencing the susceptibility gene provides a second option for achieving resistance (Fig. 4). A problem for deploying this form of plant resistance in agriculture occurs when the parasite has been clever enough to exploit a susceptibility gene that has a critical function for the plant (Dangl *et al.*, 2013; Hückelhoven *et al.*, 2013). This creates an undesirable trade-off between the harm the plant experiences by the silencing of the susceptibility gene and the benefit the plant gains by becoming resistant to the parasite. Molecular biologists hope to find ways to circumvent such trade-offs (Dangl *et al.*, 2013).

A small number of susceptibility genes have been cloned. The first was *PMR6*, which is required for the susceptibility of *Arabidopsis* to the powdery mildew pathogen *Erysiphe cichoracearum* and encodes a pectate lyase-like protein (Vogel *et al.*, 2002). The elevated expression of the *PMR6* gene induced by *E. cichoracearum* infection appears to cause a weakening of the cell wall of infected plants, with this creating favourable conditions for penetration. *pi21* is a gene that is necessary for the susceptibility of rice to the blast pathogen *Pyricularia grisea*. It encodes a proline-rich protein with a putative function as a transporter for heavy metal ions (Fukuoka *et al.*, 2009).

Several of the other cloned susceptibility genes encode proteins with nucleotide-binding and leucine-rich repeat (NBS-LRR) domains, a common structure of cloned disease/nematode/insect resistance proteins (Lorang *et al.*, 2007; Nagy and Bennetzen, 2008; Faris *et al.*, 2010). In plant–pathogen interactions, this type of gene typically triggers the hypersensitive response. The localized plant cell death that follows is harmful to biotrophic pathogens but beneficial to necrotrophic pathogens. Necrotrophic pathogens exploit this response,

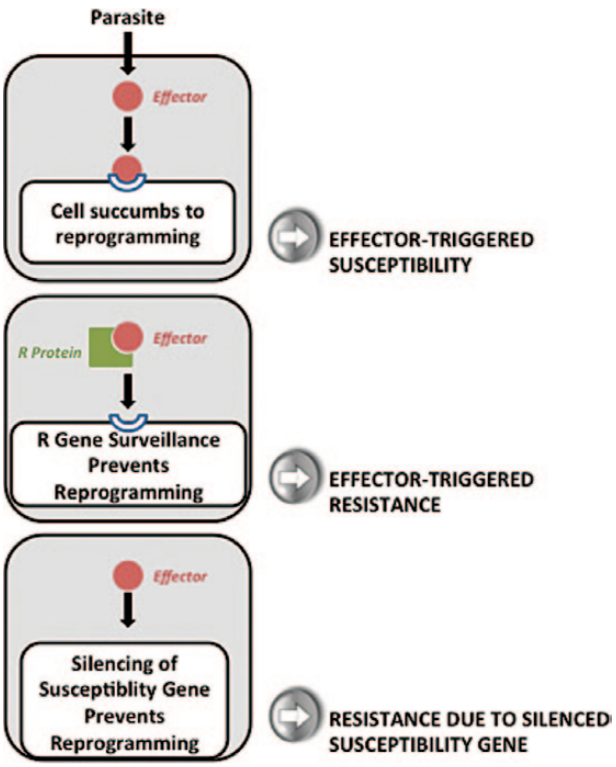

Fig. 4. The relationship between effector-triggered susceptibility and two options the plant then has for resistance. (This figure is available in colour at *JXB* online.)

specifically producing necrotrophic effectors that trigger a less contained plant cell death. This phenomenon is 'necrotrophic effector-triggered susceptibility' (NETS) (Z. Liu *et al.*, 2012, 2014). These discoveries have demonstrated that plant receptor proteins with the NBS-LRR structure can be either a resistance factor or a susceptibility factor in any given plant–parasite system, with this depending on the lifestyle of the parasite.

A gene required for wheat susceptibility to Hessian fly was identified by analysis of genes up-regulated in susceptible versus resistant plants (X. Liu *et al.*, 2013). The wheat susceptibility gene was named *Mayetiola destructor susceptibility gene one* (*Mds-1*). It encodes a small heat shock protein (hsp16.9) that is evolutionarily conserved in different organisms and has many known functions. In the absence of Hessian fly attack, *Mds-1* is not expressed in the wheat leaf sheath. Soon after Hessian fly attack of the leaf sheath begins, it is induced >100-fold. Silencing of *Mds-1* in a normally susceptible wheat genotype conferred complete resistance to all Hessian fly genotypes that were tested.

The function of *Mds-1* in wheat's susceptibility to Hessian fly is not known. No nutritive cells are formed at the feeding site in *Mds-1*-silenced plants, suggesting that *Mds-1* is required, either directly or indirectly, for nutritive cell formation. Interestingly, ectopic expression of *Mds-1* or induction by heat shock suppresses resistance of wheat mediated by *R* genes to Hessian fly. This suggests a relationship between the resistance mechanism mediated by the *R* gene and suppression of *Mds-1* expression. It also suggests that *Mds-1* has a dominant effect on *R* genes once it is expressed at high levels. The fact that *Mds-1* can be induced by heat may be a reason why the effectiveness of *H* gene-mediated resistance can be lost at elevated temperatures (Chen *et al.*, 2014*b*).

Genomes of Hessian fly and other insect herbivores

Publication of the Hessian fly genome is expected shortly (Richards *et al.*, unpublished results). The Hessian fly holds an interesting phylogenetic position between two groups of insects that have been important for genetics and functional genomics. One is the 'higher' Diptera, which includes the insect genetic model *Drosophila melanogaster*. The other is the 'lower' Diptera, which includes the mosquitoes, several of which are threats to human health. As a dipteran herbivore with a sequenced annotated genome, the Hessian fly will soon be joined by *Scaptomyza flava* (Fallen), a leaf-mining drosophilid fly whose larvae feed on wild *Arabidopsis* and other mustards in North America and Eurasia (Whiteman *et al.*, 2011). A third herbivore with a sequenced annotated genome is the pea aphid, *Acyrthosiphum pisum* (International Aphid Genomics Consortium, 2010). It differs from the Hessian fly and *Scaptomyza* in being hemimetabolous (rather than holometabolous). It is unusual in having a life cycle that shifts between generations that reproduce asexually and sexually. Another interesting feature of the pea aphid is its relationship to bacterial symbionts, which also appear to play some role in Hessian fly colonization (Bansal *et al.*, 2011). Both *A. pisum* and *S. flava* are similar to the Hessian fly in attacking at a scale that is small enough (i.e. at the scale of individual cells) to make relevant plant pathology's expanded model of plant immunity and parasite adaptation (Fig. 1). The importance of effectors is another feature shared by the pea aphid and the Hessian fly (Chen *et al.*, 2008; Bos *et al.* 2010). This is also expected to be the case for *Scaptomyza* (Whiteman *et al.*, 2011). The Hessian fly and pea aphid are both targeted by plant *R* genes. Pea aphids die on *Medicago truncatula* expressing the *RAP1* gene (Stewart *et al.*, 2009). No *R* genes have been reported for *Scaptomyza*. In contrast to the Hessian fly, the pea aphid and *Scaptomyza* have no known avirulence effectors.

Wheat and biotic stress

Cereals, including wheat (*Triticum* spp.), maize (*Zea mays* L.), and rice (*Oryza sativa* L.), have played an essential role in the rise of human civilization (Gustafson *et al.*, 2009) and will be essential for feeding the burgeoning populations of the world. Among cereals, wheat is the most important crop globally for direct consumption by humans and is also the most important source of protein for humans. Its cultivation occupies the largest crop area on Earth, 215 Mha in 2012 (http://faostat3.fao.org/faostat-gateway/go/to/home/E). For the most part, wheat cultivars belong to one of two polyploid species, hexaploid wheat (bread or common wheat, *T. aestivum*, $2n=6x=42$, AABBDD genomes) or tetraploid wheat (durum or pasta wheat, *T. turgidum* ssp. durum, $2n=4x=28$, AABB genomes). We focus on biotic stress in *T. aestivum*, and hereafter refer to it as 'wheat'.

Wheat appeared on the scene ~10 000 years ago. Ideas about how wheat evolved are shown in Fig. 5, which is based on Jauhar *et al.* (2009), and are discussed by Gustafson *et al.* (2009). Wheat is an allopolyploid; that is, a polyploid species that resulted from interspecific or intergeneric hybridization of two or more genomes from different species. Polyploidy, a common form of plant evolution, is associated with promoting the genetic diversity that facilitates adaptation to a range of environments. The way that polyploid speciation proceeded in wheat (Fig. 5) has important implications for which grass species can serve as donors and which genes can be transferred into wheat from other species and genera. Germplasm collections of diploid and polyploid species of wheat and its relatives function as vast reservoirs of potentially useful traits in the primary, secondary, and tertiary gene pools (Glaszmann *et al.*, 2010). Among these useful traits are simply inherited dominant or recessive genes that confer resistance to biotic stress.

Because wheat is a global crop, it is continually exposed to a large variety of parasite species and lineages (strains), many of which have the ability to move around the globe. The wide range of parasites that attack wheat is reviewed in a recent edited volume on wheat (Carver, 2009). Some are historical pests but others are emerging pests, such as the virulent Ug99 lineage of stem rust that originated in Africa, which is considered to have the potential to devastate global food supplies. Wheat germplasm collections have been mined extensively for resistance traits, evidence being publication of 479 wheat *R*

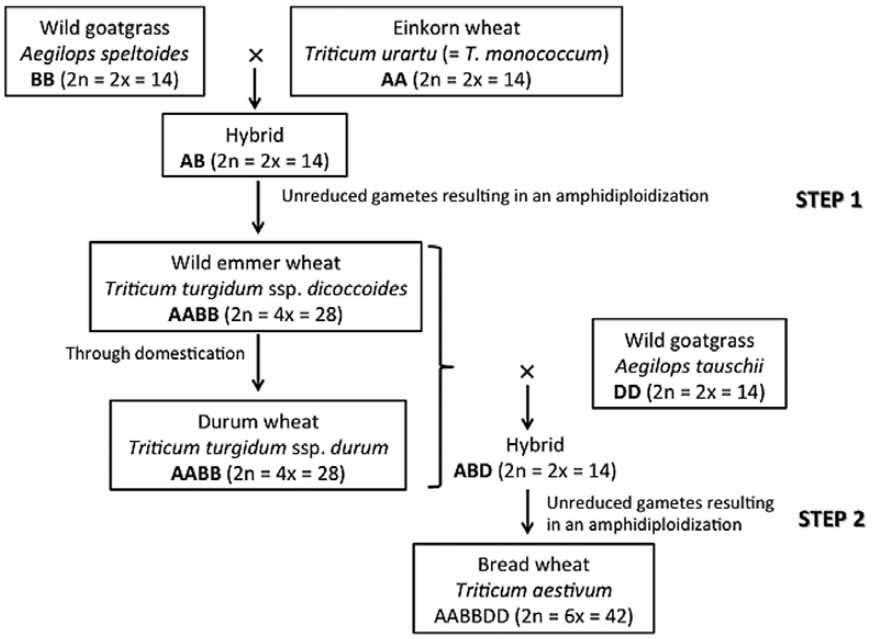

Fig. 5. Schematic representation of the evolution of hexaploid wheat *Triticum aestivum L*. (based on Jauhar *et al.*, 2009. "Reprinted by Permission, ASA, CSSA, SSSA.").

genes (Table 3). A question is: why have so many *R* genes been discovered in wheat? One reason is the low value of wheat as a crop, which makes the use of pesticides uneconomical. A second reason is the early historical success of *R* genes in protecting wheat. Today this success continues to create incentives for dissection and deployment.

Targets of the 479 *R* genes are phylogenetically diverse, ranging from simple viruses to complex animals (Table 3). Donors of the *R* genes are diverse, including species in the primary gene pool (*Triticum* spp.), secondary gene pool (e.g. *T. timopheevii*), and tertiary gene pool (e.g. *Aegilops*, *Secale*, and *Thinopyrum*). A large proportion of the published genes (79%) target fungal species, in particular powdery mildew and three rust species (Table 3). Why does wheat have so many *R* genes for these four fungal species? One reason for discovering so many *R* genes is experimental tractability, fungi being relatively easy to grow, store, and test against thousands of grass genotypes. Another reason is the wide-reaching pest status of these species, which are feared throughout the world's wheat-growing regions. Insect pests of wheat tend to be more restricted in their distribution. It is beyond the scope of this review to discuss possible evolutionary reasons why wheat has so many *R* genes for fungal pathogens.

Cloning of the *R* gene creates opportunities for exploring plant pathology's model of plant immunity (Fig. 1). So far, only nine *R* genes have been cloned from bread wheat and its relatives (Table 4). Among the nine are six *R* genes that confer race-specific plant resistance. All of the six encode proteins with an NBS-LRR domain with a coiled-coil (CC) domain. Typically this type of gene shows a greater degree of variation in LRR-encoding sequences (Ellis *et al.*, 1999; Dodds *et al.*, 2001; Yahiaou *et al.*, 2006). This is consistent with the idea that the LRR-encoding sequence is important for target specificity (Yahiaou *et al.*, 2006; Ashfield *et al.*, 2014). However, sequence variations in the NBS-encoding region can also play a role in specificity. In wheat, the *Pm3* locus encodes seven alleles (*Pm3a–Pm3g*) conferring resistance to different races of the powdery mildew pathogen (Tommasini *et al.*, 2006). Sequence analysis indicated that the *Pm3* alleles evolved either by gene conversion/recombination or by single point mutations within the NBS and LRR regions (Yahiaou *et al.*, 2006).

The three other cloned resistance genes, *Lr34*, *Yr36*, and *Pm21*, are different because they confer race-non-specific resistance (Table 4). Race-non-specific resistance is expected to be more durable when deployed in agriculture. *Lr34* confers non-specific, partial, and slow rusting resistance, and has been deployed worldwide, maintaining its effectiveness in agriculture for decades (Lagudah *et al.*, 2009). Because it confers resistance to pathogens other than leaf rust (Lr), the gene has other names, such as *Yr18*, *Pm38*, *Sr57*, and *Bdv1* for resistance to stripe rust, powdery mildew, stem rust, and barley yellow dwarf virus, respectively (Lagudah *et al.*, 2009). Map-based cloning of *Lr34* revealed a protein product similar to the ATP-binding cassette (ABC) transporters of the pleiotropic drug resistance subfamily (Krattinger *et al.*, 2009*a*). Another gene conferring race-non-specific resistance is *Yr36*, recently deployed in several bread wheat cultivars in the USA (Fu *et al.*, 2009). It encodes a protein with a predicted kinase domain and a predicted steroidogenic acute regulatory protein-related lipid transfer (START) domain (Fu *et al.*, 2009). The third gene conferring race-non-specific resistance is *Pm21*, which protects wheat against powdery mildew. It was originally transferred from *Haynaldia villosa* (L.) Schur. into wheat and it has been deployed in many Chinese wheat cultivars (Cao *et al.*, 2011). *Pm21* was identified as a candidate by a GeneChip microarray and encodes a putative serine/threonine protein kinase. Resistance conferred by *Lr34*, *Yr36*, and *Pm21* may

Table 3. *Organisms targeted by 479 wheat* R *genes, numbers of species per organism, and number of* R *genes targeted at each organism or group*

Also shown are donors of *R* genes. The four fungal species are shown separately because they are targeted by large numbers of *R* genes.

Domain, Kingdom: Phylum	Class	Species name	No. of species	No. of genes	Donors of *R* genes[a]
Virus	N/A	Various	5	12	*Ae. tauschii*, *T. aestivum*, *Th. intermedium*, *H. villosa*
Prokaryote, Bacteria: Proteobacteria	Gamma Proteobacteria	*Xanthomonas campestris* pv. *undulosa*	1	5	*T. aestivum*
Eukaryote, Fungi: Basidiomycota	Urediniomycetes	Yellow/stripe rust (*Puccinia striiformis*)	1	94	*T. aestivum*, *T. spelta*, *T. vavilovii*, *T. durum*, *T. dicoccoides*, *Ae. tauschii*, *S. cereale*, *Ae. comosa*, *Ae. geniculata*, *Ae. ventricosa*, *Ae. neglecta*, *Ae. sharonensis*, *Th. intermedium*
Eukaryote, Fungi: Basidiomycota	Urediniomycetes	Stem rust (*Puccinia graminis*)	1	65	*T. aestivum*, *T. durum*, *T. dicoccum*, *Ae. tauschii*, *S. cereale*, *Ae. speltoides*, *T. monococcum*, *T. timopheevii*, *Ae. comosa*, *Ae ovata*, *Ae. searsii*, *Ae. ventricosa*, *H. villosa*, *Th. ponticum*, *Th. intermedium*
Eukaryote, Fungi: Basidiomycota	Urediniomycetes	Leaf rust (*Puccinia triticina*)	1	79	*T. aestivum*, *T. durum*, *T. spelta*, *Ae. tauschii*, *S. cereale*, *Ae. speltoides*, *T. dicoccoides*, *T. monococcum*, *T. timopheevii*, *Ae. comosa*, *Ae. kotschyi*, *Ae. geniculata*, *Ae. umbellulata*, *Ae. ventricosa*, *Ae. triuncialis*, *Ae. sharonensis*, *Ae. neglecta*, *Ae. peregrina*, *Th. ponticum*, *Th. intermedium*, *E. trachycaulis*
Eukaryote, Fungi: Ascomycota	Leotiomycetes	Powdery mildew (*Blumeria graminis*)	1	70	*T. aestivum*, *T. sphaero-coccum*, *T. compactum*, *T. spelta*, *T. macha*, *T. durum*, *T. dicoccum*, *T. dicoccoides*, *T. carthlicum*, *T. monococcum*, *Ae. tauschii*, *T. timopheevii*, *S. cereale*, *Ae. speltoides*, *Ae. longissima*, *Ae. geniculata*, *H. villosa*, *Th. intermedium*, *Ae. umbellulata*
Eukaryote, Fungi: Various	Various	All other fungal species	12	70	*T. aestivum*, *T. compactum*, *T. durum*, *T. dicoccoides*, *T. timopheevii*, *Ae. tauschii*, *Ae. ventricosa*, *H. villosa*, *L. racemosus*
Eukaryote, Animals: Nematoda	Secernentea	Various	3	15	*Ae. tauschii*, *Ae. variabilis*, *Ae. ventricosa*, *T. aestivum*, *S. cereale*
Eukaryote, Animals: Arthropoda	Insecta	Various	5	65	*Ae. speltoides*, *Ae. tauschii*, *Ae. triuncialis*, *Ae. ventricosa*, *T. aestivum*, *T. durum*, *Th. elongatum*, *S. cereale*
Eukaryote, Animals: Arthropoda	Arachnida	Various	1	4	*Ae. tauschii*, *S. cereale*, *Th. elongatum*

[a] Abbreviations for genus: *Ae.*, *Aegilops*; *E.*, *Elymus*; *H.*, *Haynaldia*; *L.*, *Leymus*; *S.*, *Secale*; *T.*, *Triticum*; *Th.*, *Thinopyrum*.
Source: McIntosh *et al.* (2013).

Table 4. *Nine cloned wheat* Resistance *genes that confer resistance to pathogens*

The ninth gene, *Lr34*, is unusual in conferring resistance to multiple plant pathogens and has additional names, namely *Yr18*, *Sr57*, *Pm38*, and *Bdv1* for resistance to yellow rust, stem rust, powdery mildew, and barley yellow dwarf virus, respectively.

Disease	*R* gene	Donor species (chromosome location)	Markers	Gene product	Resistance type	Status in agriculture	References
Stem rust *Puccinia graminis*	*Sr33*	*Ae. tauschii* (1DS)	*Xbarc152*, *Xcfd15*	NBS-LRR-CC	Race specific	Not deployed	Sambasivam *et al.* (2008); Periyannan *et al.* (2013)
	Sr35	*T. monococcum* (3AS)	*Xcfa2170*, *XAK335187*	NBS-LRR-CC	Race specific	Not deployed	Saintenac *et al.* (2013)
Leaf rust *Puccinia triticina*	*Lr1*	*T. aestivum* (5DL)	*Xpsr567*, *Xabc718*	NBS-LRR-CC	Race specific	Present in a number of cultivars	Cloutier *et al.* (2007); Qiu *et al.* (2007)
	L10	*T. aestivum* (1AS)	*Xsfr1*, *Xsfrp1*	NBS-LRR-CC	Race specific	Present in old cultivars in Australia, Canada, and the USA	Schachermayr *et al.* (1997); Feuillet *et al.* (2003)
	Lr21	*Ae. tauschii* (1DL)	*XksuD14*, *Xksu936*, *Xksu937*	NBS-LRR-CC	Race specific	Deployed in many US cultivars	Huang *et al.* (2003)
Yellow/stripe rust *Puccinia striiformis*	*Yr36*	*T. dicoccoides* (6BS)	*Xucw125*, *Xucw130*	Wheat kinase-START-1	Adult plant resistance	Deployed in a few US cultivars	Fu *et al.* (2009)
Powdery mildew *Blumeria graminis*	*Pm3* (alleles: *Pm3a*, *Pm3b*, *Pm3c*, *Pm3d*, *Pm3e*, *Pm3f*, *Pm3g*)	*T. aestivum* (1AS)	*Pm3a*, *Pm3b*, *Pm3c*, *Pm3d*, *Pm3e*, *Pm3f*, *Pm3g* (allele-specific)	NBS-LRR-CC	Race specific	Alleles *Pm3a* and *Pm3g* are present in many European cultivars, while *Pm3b*, *Pm3c*, *Pm3e*, and *Pm3f* are present in a few European cultivars. *Pm3a* is also present in many US cultivars	Yahiaoui *et al.* (2004); Srichumpa *et al.* (2005); Tommasini *et al.* (2006)
	Pm21	*H. villosa* (6VS)	*NAU/Xibao15*	Serine/threonine kinase	Durable, broad-spectrum resistance	Widely deployed in China	Cao *et al.* (2011)
Multiple diseases (leaf, stripe, and stem rusts, powdery mildew, and barley yellow dwarf virus)	*Lr34* (*Yr18*, *Sr57*, *Pm38* *Bdv1*)	*T. aestivum* (7DS)	*Ltn* (*leaf tip necrosis*), *Xcssfr1–Xcssfr6* (allele-specific)	ABC transporter	Adult plant resistance	Deployed worldwide	Lagudah *et al.* (2009); Krattinger *et al.* (2009a)

represent a heterogeneous group of genes and mechanisms (Fu *et al.*, 2009) that do not fit the gene-for-gene model (Cao *et al.*, 2011). Given the two very different types of plant resistance conferred by the nine cloned wheat *R* genes, it will be interesting to see if this necessitates modification of plant pathology's model of plant immunity (Fig. 1).

Wheat has *R* genes that target a number of arthropod pests, including the Hessian fly (Table 5). All the targets are species that are expected to attack with greater stealth, including two cecidomyiids, three aphids, and an eriophyid mite. No *R* genes have been reported for other cecidomyiid and aphid species that attack wheat. In Europe (Barnes, 1956), these other species include the lemon wheat blossom midge, *Contarinia tritici* (Kirby), and the saddle gall midge, *Haplodiplosis marginata* (von Roser). Worldwide, this includes the bird cherry oat aphid *Rhopalosiphum padi* L. (Hemiptera: Aphididae) (Dunn *et al.*, 2007). All species in Table 5 are likely to have an effector-based strategy of induced susceptibility, this being suggested by dramatic growth effects on the plant. A number of the species are vectors of plant viruses that pose significant challenges for wheat production. Donors of the *R* genes targeted at arthropods come from wheat's primary and tertiary gene pools (Table 5). While many of the wheat *R* genes targeted at arthropods have genetic markers that are used by plant breeders, none have been cloned.

Table 5. *Insects and mites targeted by wheat resistance and* Resistance *genes*

None of the *R* genes has been cloned.

Insect	Total *R* genes	Donor(s) and chromosome	*R* genes having markers	Status	References
Hessian fly *Mayetiola destructor* Say INSECTA DIPTERA: CECIDOMYIIDAE	*H* genes, *n*=37	*T. aestivum* (1AS) *T. durum* (1AS) *Ae. tauschii* (3DL, 6DS) *T. dicoccom* (1AS)	*H3*, *H5*, *H6*, *H9*, *H10*, *H11*, *H13*, *H14*, *H16*, *H22*, *H23*, *H24*, *H26*, *H31*, *H32*, *H33*, *H34*, *Hdic*	Small number deployed in many US cultivars; *H13* deployed in US cultivar INW9811Õ; most not deployed yet or at least not deployed knowingly	McIntosh *et al.* (2013); Li *et al.* (2013); McDonald *et al.* (2014)
Orange wheat blossom midge *Sitodiplosis mosellana* INSECTA DIPTERA: CECIDOMYIIDAE	*Sm* gene *n*=1	*T. aestivum* (2BS)	*Sm1*	Widely deployed in many Canadian and UK cultivars	McIntosh *et al.* (2013); Thomas *et al.* (2005)
Greenbug *Schizaphis graminum* (Rondani) INSECTA HEMIPTERA: APHIDIDAE	*Gb* genes, *n*=15	*S. cereale* (T1BL.1RS) *Ae. tauschii* (7DL)	*Gb2*, *Gb3*, *Gb6*, *Gb7*, *Gba*, *Gbb*, *Gbc*, *Gbd*, *Gbx1*, *Gbx2*, *Gby*, *Gbz*	Vector: *Barley yellow dwarf virus*; deployed in US cultivars Amigo, TAM107, TAM 110, TAM112, TAM 200, TAM202, Century	McIntosh *et al.* (2013); Graybosch *et al.* (1999); Azhguvel *et al*. (2012); Rudd *et al.* (2014); S. Liu *et al.* (2014)
Russian wheat aphid *Diuraphis noxia* (Mordvilko) INSECTA HEMIPTERA: APHIDIDAE	*Dn* and *dn* genes, *n*=11	*T. aestivum* (7DS, 1DL) *Ae. tauschii*	*Dn1*, *Dn2*, *Dn4*, *Dn5*, *Dn6*, *Dn7*, *Dn8*, *Dn9*, *Dnx*, *Dn1881*	Deployed in many cultivars in South Africa and USA (Colorado)	McIntosh *et al.* (2013); S. Liu *et al.* (2014)
English grain aphid *Sitobion avenae* (F.) INSECTA HEMIPTERA: APHIDIDAE	*Sa*, *n*=1	*T. durum* (6AL)	*Sa1*	Vector: *Barley yellow dwarf virus*	McIntosh *et al.* (2013); Liu *et al.* (2012)
Wheat curl mite *Aceria tosichella* ARACHNIDA PROSTIGMATA: ERIOPHYIDAE	*Cmc* (curl mite colonization), *n*=4	*Ae. tauschii* (6DS) *S. cereale* (1RS) *Th. elongatum* (6AeS)	*Cmc3*, *Cmc4*	Vector: *Wheat streak mosaic virus*; deployed in US cultivars Amigo, TAM107	McIntosh *et al.* (2013); Malik *et al.* (2003); S. Liu *et al.* (2014)

Map-based cloning in wheat has been extraordinarily difficult due to wheat's large genome (17 Gigabase) and the density and distribution of repetitive sequences in that genome. Non-coded highly repeated DNA sequences comprise up to 90% of the genome (Arumuganathan and Earle, 1991; Li *et al.*, 2004; International Wheat Genome Sequencing Consortium, 2014). Despite considerable effort, only 16 targeted wheat genes have been positionally cloned (Table 6). Cloning wheat genes will be easier in the future because of recent progress in wheat genomics and an expanding set of genetic resources (Table 6), including expressed sequence tags (ESTs) and molecular markers, high-density integrated genetic maps, physical maps, BAC libraries, genetic stocks, and draft genome sequences. The benefits of genomics for cloning crop *R* genes is clear from the example of rice, where many *R* genes targeted at the brown planthopper have been and are being cloned (Du *et al.*, 2009; Tamura *et al.*, 2014).

Closing thoughts

In our review we first argue for the incorporation of arthropods into plant pathology's expanded model of plant immunity and parasite adaptation. Is the model overly simplistic? Given their dazzling progress toward understanding plant biotic stress, the answer for plant pathology is clearly no. The answer for entomology is less clear. The model may indeed be too simplistic for some insect herbivores, particularly those for which speed and brute force are the essence of attack (Howe and Jander, 2008; Erb *et al.*, 2012). On the other hand, we, as well as others, believe it is useful for arthropods that attack with greater stealth (Walling, 2000; Harris *et al.*, 2003; Kaloshian and Walling, 2005; Hogenhout and Bos, 2011). While the stealthy species do not represent all arthropods, neither do the brute force species. Arthropod herbivores are notoriously diverse. In terms of applied science, arthropods that attack with greater stealth are significant pests of agriculture. Moreover they

Table 6. *Genetic and genomic resources of wheat*

Types	Details and References[a]
Markers and ESTs	~3600 SSRs (1); ~7000 DArT (2); 90 000 SNPs (3); 416 856 GBS (4); 1 286 372 ESTs (5), and ~6000 bin-mapped ESTs (6).
Integrated genetic maps	SSR consensus map: 1235 SSRs (7); Reference map: 416 856 GBS markers, 2740 gene-derived SNPs, 1351 DArTs, 118 SSRs/STSs (4); High-density SNP map: 46 977 SNPs (3)
Physical maps	*T. aestivum* chromosome 3B (8); *Ae. tauschii* D genome (9)
BAC clones	Nine BAC libraries containing 3 576 192 clones from *Ae. tauschii*, *T. monococcum*, *T. durum*, and *T. aestivum* (6, 10).
Genetic stocks	102 telosomics, 21 monosomics, 21 trisomics, 38 nullisomic–tetrasomics, 184 single chromosome substitution lines, 436 segmental deletion lines (6).
Gene mapping and cloning	Over 10 000 unigenes and hundreds of QTLs have been mapped; 16 genes, *Lr1*, *Lr10*, *Lr21*, *Q*, *Vrn1*, *Vrn2*, *Vrn3*, *Ph1*, *Gpc-B1*, *Pm3*, *Lr34*, *Yr36*, *Tsn1*, *Sr33*, *Sr35*, and *TaPHS1*, were positionally cloned (11–17), and one gene *Pm21* was cloned using a GeneChip microarray (18)
Genome sequences	*T. aestivum* low-coverage and long-read shotgun sequences (19), *T. aestivum* chromosome-based draft sequence (20), *T. urartu* A genome (21), *Ae. tauschii* D genome (22), and *T. aestivum* chromosome 3B genome sequences (23).

[a] References: (1) https://www.integratedbreeding.net/298/breeding-services/predictive-markers; (2) L. Zhang *et al.* (2011); (3) Wang *et al.* (2014); (4) Saintenac *et al.*, 2013; (5) http://www.ncbi.nlm.nih.gov/genbank/dbest/dbest_summary/; (6) Gill *et al.* (2004); (7) Somers *et al.* (2004); (8) Paux *et al.* (2008; (9) Luo *et al.* (2013); (10) Moullet *et al.* (1999); (11) see review by Krattinger *et al.* (2009*b*) for map-based cloning of *Lr1*, *Lr10*, *Lr21*, *Q*, *Vrn1*, *Vrn2*, *Vrn3*, *Ph1*, *Gpc-B1*, and *Pm3*; (12) Krattinger *et al.* (2009*a*); (13) Fu *et al.* (2009); (14) Faris *et al.* (2010); (15) Periyannan *et al.* (2013); (16) Saintenac *et al.* (2013); (17) S. Liu *et al.* (2013); (18) Cao *et al.* (2011); (19) Brenchley *et al.* (2012); (20) International Wheat Genome Sequencing Consortium (2014); (21) Ling *et al.* (2013); (22) Jia *et al.* (2013); (23) Choulet *et al.* (2014).

represent a significant proportion of the world's agricultural pests that, at this point in time, are not controlled by genetically engineered (GE) transgenic traits. This contrasts with the successful GE control of several of the world's most famous brute force insects, many of which are caterpillars. The second thing we argue for in this review is a research initiative on integrated biotic stress in wheat. Wheat has 479 documented *R* genes. Genome sequencing of *T. aestivum* is progressing at a rapid pace, making likely the cloning of many wheat genes in the near future. New genetic technologies, such as TILLING (Targeting Induced Local Lesions IN Genomes), will permit more precise and efficient characterization of the function of targeted wheat genes (Rawat *et al.*, 2012). This is creating a great deal of excitement in the wheat community. We have all seen the power of an integrated approach to plant biotic stress in *Arabidopsis thaliana*. Duplicating this effort for wheat has obvious benefits for science and agriculture. Borrowing language from an important review by Dangl *et al.* (2013), it is time to pivot the plant immune system from dissection to deployment.

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