

Review

Genomic Clues for Crop–Weed Interactions and Evolution

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Agronomically critical weeds that have evolved alongside crop species are characterized by rapid adaptation and invasiveness, which can result in an enormous reduction in annual crop yield worldwide. We discuss here recent genome-based research studies on agricultural weeds and crop–weed interactions that reveal several major evolutionary innovations such as de-domestication, interactions mediated by allelochemical secondary metabolites, and parasitic genetic elements that play crucial roles in enhancing weed invasiveness in agricultural settings. We believe that these key studies will guide future research into the evolution of crop–weed interactions, and further the development of practical applications in agricultural weed control and crop breeding.

Crops and Weeds

Agronomically important weeds cause tremendous losses of crop yields worldwide and have evolved to exploit croplands through a variety of different mechanisms that confer strong adaptive and competitive abilities [1,2]. Among crop pests, agricultural weeds are estimated to account for approximately one third of all yield loss (~34%), far more than either animal pests (~18% loss) or plant pathogens (~16% loss) [3]. **Crop–weed interactions** (see Glossary) have long been an important topic in the study of agronomics [4]. Complementing this applied research focus is the increasing recognition of agricultural weeds as fascinating models for studying the adaptation and rapid evolution of plant species in human-mediated environments [1,2].

The emergence of agriculture ~12 000 years ago created fertile new habitats not only for the cultivated species that were intentionally planted there but also for unwanted species that adapted to exploit this new environment. In some cases these weed species are closely related to cultivated crops; these may include wild relatives as well as feral descendants of crops, also called weedy crop relatives, which have evolved through **de-domestication**. In many other cases agricultural weeds are wild species with no close relationship to domesticates, and are therefore referred to as weedy non-crop relatives (Figure 1). Both types of weed are characterized by the ability to aggressively compete for resources in the agricultural environment, and to proliferate through adaptations such as prolonged seed dormancy, rapid growth rates, ease of dispersal, and herbicide resistance. These adaptations are collectively referred to as the **agricultural weed syndrome** [1]. From the perspective of a weed, crop species, humans, and the other biotic and abiotic stresses present in the agroecosystem are all important environmental factors influencing their ecology and evolution. Crops and agricultural weeds have complex ecological and evolutionary interactions which play out exclusively in the agricultural environments created by humans.

An understanding of the evolution of agricultural weeds and crop–weed interactions will be crucial for improving weed management and crop breeding. For example, taking advantage of our knowledge of crop–weed interactions to develop competitive crop cultivars via breeding is

Highlights

Agricultural weeds can be generally classified into weedy crop relatives and non-crop relatives based on their genetic relationship to crops. They are not only economically important but are fascinating models for studying the adaptation and rapid evolution of plant species in human-mediated environments.

Allelopathy by secondary metabolites is a central process underlying crop–weed interactions in agroecosystems. Biosynthetic gene clusters may be one important genomic mechanism governing these allelopathic interactions.

Genetic exchanges occur frequently between crops and parasitic weeds, and can evidently have functional consequences.

Recent genomic studies of weedy plants are providing in-depth insights into the evolution of weeds and the mechanisms of crop–weed interactions, and are likely to have a major impact on weed management and crop breeding.

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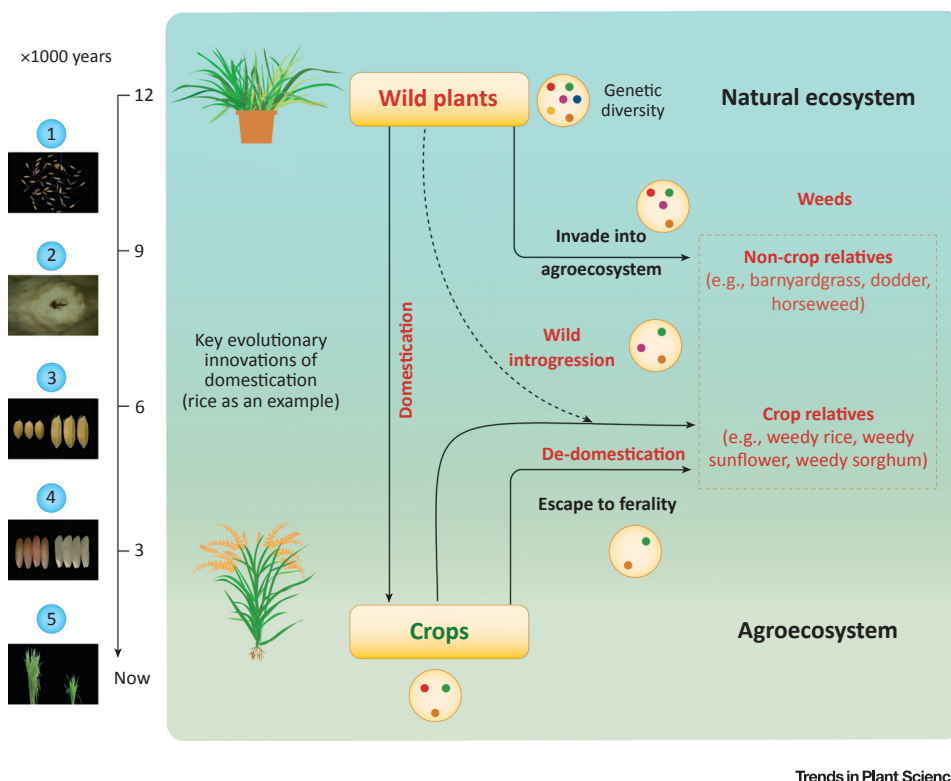


Figure 1. The Evolutionary Relationships between Wild Plants, Crops, and Weeds. The different origins of agricultural weeds from wild plants and crops are illustrated. Weeds derived from wild plants are termed weedy non-crop relatives, and their wild progenitors invaded and adapted from natural ecosystems into agroecosystems, with some loss of genetic diversity (as indicated by differently colored dots in grey circles). Weedy crop relatives are de-domesticated forms of crops. During their escape to fertility a severe genetic bottleneck occurs. In addition, the de-domesticated weeds may introgress with their wild progenitors to enhance their diversity and adaptation. (1–5) Several key evolutionary innovations of rice domestication are highlighted (initial seed collection or the start of domestication, domesticated type of spikelet base causing non-shattering, increase in grain size, the development of white pericarp, and semi-dwarf plants, respectively).

an efficient and environmentally friendly approach to integrated weed management [5]. However, the molecular mechanisms underlying the rapid adaptation and evolution of weedy plants in crop fields are still not well understood. Reference plant genomes have provided novel insights into the physiological and evolutionary processes by which plant species respond to their environments [6]. However, despite the major economic impact of agricultural weed species, few genomic-scale analyses have been performed [7] (Table 1). Genome-based studies on weeds and crop–weed interactions have been anticipated for a long time [8,9], but insights into crop–weed interactions remain one-sided, mostly skewed towards crop species. Fortunately, an emerging number of recent genome-based investigations of weed species are beginning to reveal novel insights into weed evolution and crop–weed interactions [10–15]. This review focuses on recent genomic insights on the evolution of agricultural weeds, with a special emphasis on the interactions between crop and weed.

Evolution of Weedy Crop Relatives and Non-Crop Relatives

The weedy crop relative, an important category of agricultural weeds, has gained attention in recent years for its ability to cause tremendous crop yield loss. The evolutionary history of

Glossary

Agricultural weed syndrome: the adaptive traits enabling agricultural weeds to survive and thrive vary from species to species, and these include rapid growth, high nutrient use efficiency, seed dormancy, efficient seed dispersal, crop mimicry, and herbicide resistance.

Adaptive introgression: incorporation of alleles from one species into the gene pool of another divergent species. Such introgressed alleles could increase the fitness of the species, and are maintained by natural selection.

Allelopathy: antagonistic chemical interactions and competitions between plants, a common phenomenon to inhibit or stimulate the growth of neighbors in the environment by exuding natural chemical compounds (allelochemicals), which are primarily secondary metabolites.

Balancing selection: a selective process by which genetic polymorphisms are actively maintained in the gene pool of a population at frequencies larger than expected from genetic drift alone. Three main mechanisms include (i) heterozygote advantage, (ii) frequency-dependent selection in which rare genotypes have a fitness advantage, and (iii) selection varying in space and time, in which case different genotypes have an advantage in different environments.

Biosynthetic gene cluster: a group of closely linked non-homologous genes encoding enzymes that are collectively responsible for the sequential biosynthesis of a secondary metabolite. Genes with in a cluster are transcribed into independent mRNAs. A gene cluster consisting of a ~100 kb region typically contains at least three non-homologous genes encoding components of the same pathway. CYP genes are often involved in secondary metabolite biosynthesis.

Crop–weed interactions: weeds interact with crops in various ways, including chemical interactions, competition for resources, and host–parasite genetic crosstalk. These interactions occur at an ecological timescale but may result in adaptive changes at an evolutionary timescale.

weeds of this type is believed to start from the earliest day of agriculture, and now the 25 most important crops in the world are reported to have weedy relatives [16], among which three examples are discussed further, including rice with weedy rice (*Oryza sativa* f. *spontanea*), sorghum with shattercane (*Sorghum bicolor* ssp. *drummondii*), and wheat with the jointed goatgrass (*Aegilops cylindrica*) and Tausch's goatgrass (*Aegilops tauschii* Coss.).

Weedy rice is the best-studied weedy crop relative. All present-day cultivated varieties of Asian rice (e.g., *O. sativa* ssp. *indica* and *japonica*) were domesticated from *O. rufipogon* (including its annual form, *O. nivara*) around 10 000 years ago [17–19]. As a companion of cultivated rice, weedy forms of rice likely emerged in the earliest days of rice domestication [11], and both US and Chinese weedy rice de-domesticated independently and repeatedly during the history of rice cultivation [11,12,20]. Similarly to domestication, there were severe **genetic bottlenecks** during the de-domestication process [12,21]. In addition, weeds that evolved through de-domestication followed by **adaptive introgression** from wild relatives pose especially difficult challenges for detection and management [2]. The continuous adaptation of weedy strains to diverse anthropogenic environments, with mutual gene flow to and from wild relatives in some geographical regions, has led to the formation of a genetically and morphologically variable group. Collectively, weedy rice strains possess a suite of traits that are intermediate between wild and cultivated rice [22]. Genetic surveys around the world suggest that all these weedy rice strains with adaptive introgression, including forms that closely resemble the crop ('crop-mimic' forms) as well as those with more **wild-like traits**, show at least some degree of ancestry from cultivated rice varieties [23–26].

The species *Sorghum bicolor* consists of three morphologically different subspecies, ssp. *bicolor* (cultivated sorghum), ssp. *drummondii* (with two weedy forms, sudangrass and shattercane), and ssp. *arundinaceum* (common wild sorghum) [27]. Cultivated sorghum was primarily domesticated from its wild progenitor *Sorghum bicolor* ssp. *arundinaceum* in north-eastern Africa [28,29]. Sudangrass and shattercane are common weeds in many sorghum production areas around the world. Morphological and genetic surveys suggested that both weedy sorghum types evolved through hybridization between cultivated and wild sorghum [30]. Similarly, the johnsongrass (*S. halepense*) and columbusgrass (*S. alnum*) are also widely found in sorghum fields and often hybridize with the cultivated sorghum species [30].

Finally, jointed goatgrass and Tausch's goatgrass are examples of weedy crop relatives of domesticated wheat. The hexaploid wheat (*Triticum aestivum*) ($2n = 6 \times = 42$, AABBDD) was domesticated in the Middle East around 10 000 years ago [31]. Jointed goatgrass (*Aegilops cylindrica*) ($2n = 4 \times = 28$, CCDD) is an aggressive weedy species of Eurasian origin that is now rapidly expanding in the wheat fields of North America [32]. Tausch's goatgrass (*Aegilops tauschii* Coss.) ($2n = 2 \times = 14$, DD), is an invasive and economically important grass weeds in winter wheat-producing areas [33]. Because the weeds and wheat have similar phenological and morphological characteristics, and share the D subgenome (derived from *Aegilops tauschii*), interspecific hybridization followed by backcross to either parental species occurs occasionally under natural field conditions [34]. Such interspecific hybridizations and backcrosses can transfer fitness advantage traits (e.g., herbicide resistance) to the weeds [34].

Unlike weedy crop relatives, weedy non-crop relatives are often generalists; they are pre-adapted to invade crop fields, which causes significant crop loss (Figure 1). As they invade the agroecosystem, the weeds are subject to continuous and diverse selective pressures to develop mechanisms to avoid removal from agricultural fields. A representative non-crop relative weed, *Echinochloa* species, is notorious for competing with important crops such as rice, maize,

Cytochrome P450 (CYP) and glutathione S-transferase (GST):

two enzymes associated with the endoplasmic reticulum that among other functions catalyze detoxification of lipophilic compounds by mono-oxygenation or glutathione conjugation, interact with reactive oxygen species, and play key roles in conferring resistance to herbicides.

De-domestication: the evolution of agricultural weeds from domesticated crop ancestors. This process selects for traits that allow the weedy derivative to survive and persist in agricultural fields without active human cultivation. Some but not all of these adaptations involve phenotypic reversions from domestication traits to the characteristics of crop wild ancestors (e.g., re-emergence of seed shattering and dormancy). Others are traits that are not characteristics of wild species but confer a competitive success specifically in agroecosystems (e.g., competitive nutrient uptake, ability to rapidly outgrow cultivated crops, crypsis in agricultural fields).

DIMBOA: 2,4-dihydroxy-1,4-benzoxazin-3-one, a benzoxazinoid defense compound synthesized by a gene cluster in maize and barnyardgrass; benzoxazinoid is also biosynthesized by other Poaceae species, such as wheat, but these species lack a complete gene cluster.

Horizontal gene transfer (HGT):

the movement of genetic material between organisms via pathways other than the transmission of DNA from parent to offspring, or Mendelian heredity.

Genetic bottleneck: a genetic bottleneck occurs when some events (e.g., environmental changes or human interference) greatly reduce the number of individuals of a species. Large amounts of genetic diversity are lost when a population shrinks to only a few individuals.

microRNAs (miRNAs): small non-coding RNA molecules encoded by non-coding genes that function in RNA silencing and post-transcriptional regulation of gene expression.

Parasitism: a relationship between species where one organism, the parasite, lives on or in another

sorghum, and soybeans. Competition from the most pervasive *Echinochloa* species, *E. crus-galli* (barnyardgrass), causes ~35% of rice yield loss worldwide [35,36]. The evolution of its weediness traits (e.g., rice mimicry and herbicide resistance) occurred in parallel with the domestication of rice and the development of agricultural weed management. The domestication of rice has led to its erect plant architecture; weed management led to the evolution of the same erect architecture in some weeds. During early agricultural times, hand-weeding was commonly performed to get rid of weeds in rice fields. Barnyardgrass weeds phenotypically distinct from rice were easily removed, while those with similar phenotypes remained in the fields. Consequently, some such weeds have also evolved the erect plant architecture and other rice mimic traits, through unintended artificial selection [37]. As a result, the *Echinochloa* species is the best-characterized plant for crop mimicry. With the shift of weed management from traditional hand-weeding to modern herbicides, *E. crus-galli* has also evolved herbicide resistance and is included among the most dangerous herbicide-resistant weeds in the world [38].

Genomic and Evolutionary Mechanisms Underlying the Establishment of Weediness Traits

Given the diverse and complicated evolutionary history of agricultural weeds, it is possible that diverse genetic mechanisms underlie the weediness trait. In the case of the rice and its weedy relative, archeobotanical remains and genetic data indicate that the non-shattering or reduced-shattering alleles (e.g., the *sh4* reduced-function allele) were fixed in cultivated rice at least 6600–6900 years ago (reviewed in [39,40]) (Figure 1). However, despite the high shattering phenotype of weedy rice, most weedy strains harbor the domesticated or non-shattering alleles. Therefore, the seed-shattering phenotype of the weeds appears to have evolved through genomic mechanisms other than simple back-mutations to the shattering alleles [23,41–43]. Unfortunately, the shattering mechanism of weedy rice remains to be elucidated, although quantitative trait locus (QTL)-based investigations have sought to locate the candidate loci [44].

Herbicide resistance (HR) is a common weed feature that has evolved in parallel within many notorious agricultural weeds [45]. The widespread use of chemical herbicides and the development of many HR crop varieties over the past 65 years has led to the rapid evolution of >400 HR weed species worldwide [38,46]. For example, many weed species in the family Poaceae have evolved glyphosate-resistance traits, possibly owing to greater exposure to glyphosate and effective selection for glyphosate resistance [45]. The HR weeds rigid ryegrass (*Lolium* sp.), Indian goosegrass (*Eleusine indica*), johnsongrass (*S. halepense*), and crabgrass (*Digitaria sanguinalis*) are commonly found in crop fields worldwide [45], and have rapidly evolved multiple HR traits through both **target-site and non-target-site mechanisms** [46,47] (Table 1).

Population genomic studies based on genome resequencing have greatly improved our understanding of the genetic basis of weedy species adaptation [11,12,48]. Of the two major weed strains grown in the USA, which evolved independently from different crop ancestors, only ~3% of the genome of each strain showed evidence of selective sweeps during domestication, some of which overlap with previously identified QTLs for weediness [11,44]. Whereas a suite of weediness traits (e.g., seed shattering, dormancy, red pericarp) are common to both of the strains, only 0.3% of the genomic regions that show signatures of selection during weed evolution overlap between the two genomes. As with the US weedy rice, genome-wide screening of *indica*- and *japonica*-like weedy rice strains in China also found a low rate of overlapping. Notably, it has been observed that one genomic region repeatedly targeted by selection in Chinese weedy rice contains a cluster of seed allergenic genes [12]. Although both *indica*- and *japonica*-like weedy strains have experienced strong genetic bottlenecks, some divergent genomic regions in weed species exhibit relatively higher nucleotide

organism, the host, causing it some harm, and is adapted structurally to this way of life.

Target-site and non-target site mechanisms: mechanisms of resistance to herbicides are generally categorized as being either 'target site' or 'non-target site' in nature. Target-site resistance may involve structural modifications of a target enzyme caused gene mutations. For non-target site mechanisms, the number of herbicide molecules reaching the target site is reduced. The mechanism often involves enhanced rates of herbicide metabolism or export via CYP, ABC transporter, GST, glycosyltransferase (GT) and peroxidase (POD) enzymes.

Wild-like traits: traits similar to those exhibited by wild plants, such as seed shattering, dark seed color, and seed dormancy.

Table 1. Genomic and Evolutionary Features of Weeds Associated with Staple Food Crops around the World^a

Crops	Weed (common name)	Weed (latin name)	Origin type	Genome sequencing	Genomic evolutionary features	Refs
Maize	Pigweed	<i>Amaranthus palmeri</i>	Non-crop relative	Transcriptomes	Amplification of the <i>EPSPS</i> gene	[99]
	Goosefoot	<i>Chenopodium album</i>	Crop relative	Segment or partial (EST)	NA	[100]
	Galinsoga	<i>Galinsoga parviflora</i>	Non-crop relative	Transcriptomes	NA	[101]
Rice	Barnyardgrass	<i>Echinochloa</i> complex	Non-crop relative	Draft genome	Biosynthetic gene cluster; CYPs and GSTs are over-represented	[13]
	Weedy rice	<i>Oryza sativa</i> f. <i>spontanea</i>	Crop relative	Re-sequencing	De-domestication; balancing selection	[11,12]
	Rice flatsedge	<i>Cyperus iria</i>	Non-crop relative	Transcriptomes	ALS-inhibiting herbicide resistance	[102]
Wheat	Rigid ryegrass	<i>Lolium rigidum</i>	Non-crop relative	Transcriptomes	Metabolic resistance	[103]
	Jointed goatgrass	<i>Aegilops cylindrica</i>	Crop relative	Transcriptomes	Abundant transposable elements	[104]
	Wild oat	<i>Avena fatua</i>	Crop relative	Transcriptomes	Metabolic resistance	[105]
Soybean	Crabgrass	<i>Digitaria sanguinalis</i>	Non-crop relative	Transcriptomes	High ACCase gene copy number	[106]
	Horseweed	<i>Conyza canadensis</i>	Non-crop relative	Draft genome	CYPs are over-represented	[10]
	Dodders	<i>Cuscuta</i> spp.	Non-crop relative	draft genome	HGT; large-scale gene losses	[14,15]
Sorghum	Johnsongrass	<i>Sorghum halepense</i>	Crop relative	Transcriptomes	Extensive over-wintering rhizome system	[107]
	Shattercane	<i>S. bicolor</i> spp. <i>drummondii</i>	Crop relative	Re-sequencing	De-domestication; high gene flow	[108]
	Bermudagrass	<i>Cynodon dactylon</i>	Non-crop relative	Transcriptomes	NA	[109]
Potatoes	Crabgrass	<i>Digitaria sanguinalis</i>	Non-crop relative	Transcriptomes	Increased ACCase gene copy number	[106]
	Chickweed	<i>Stellaria media</i>	Non-crop relative	Transcriptomes	High copy numbers of antimicrobial peptide genes	[110]
	Indian goosegrass	<i>Eleusine indica</i>	Non-crop relative	Transcriptomes	Metabolic glyphosate resistance	[111]
Other weeds with available genome sequences	Wild radish	<i>Raphanus raphanistrum</i>	Crop relative	Draft genome	Functional divergence between genome duplications	[112]

^aAbbreviations: ACCase, acetyl CoA carboxylase; ALS, acetolactate synthase; NA, not available.

diversity than their crop ancestors. This observation indicates that **balancing selection** might have acted on these regions, which would therefore be expected to help to maintain high polymorphism in the adaptation-related genes and provide an evolutionary mechanism for adaptations during weed evolution [12].

A Genomic Perspective on Crop–Weed Interactions

Plant–plant interactions are an important but poorly understood component of plant biotic interactions [49]. Aspects of plant–plant interactions include resource competition (for nutrients, light, and water), direct and indirect interactions via microbial communities, **allelopathy**, and **parasitism**. In the particular case of crop–weed interactions, allelopathy and crop–parasitic weed interactions represent two largely unexplored forms of interactions; however, several interesting genomic and evolutionary findings have emerged in recent years, which we discuss below.

Allelopathy and Biosynthetic Gene Clusters

Allelopathy is regarded as a biochemical mechanism for crop–weed interaction [50,51]. Allelopathic potential can contribute to species distribution patterns and plays a crucial role in the invasive success of weedy plants [52]. Several secondary metabolites produced by plants have been identified as potential putative natural chemical compounds (allelochemicals), and these include many types of phenolic acids, phenyl-alkanoic acids, hydroxamic acids, fatty acids, terpenes, and indoles [53]. Such compounds may play defensive roles by acting as ‘allelopathic weapons’ that inhibit or stimulate the growth of neighboring plant species [54]. Induced by biotic and abiotic factors, the biosynthesis and exudation of these metabolites follow a distinct temporal and dynamic pattern [55–57]. Numerous studies determining the genetic mechanisms associated with crop–weed interactions [13,58,59] have shown that the allelopathic effects are highly complex. These have been categorized into physiological and ecological effects, such as inhibition of cell division and elongation, disruption of antioxidant systems, increasing cell-membrane permeability, and effects of allelochemicals on microorganisms and the immediate environment [60].

One interesting trend that has emerged recently is the clustering of non-homologous biosynthetic genes for some allelochemicals (e.g., benzoxazinoids, cyanogenic glucosides, terpenoids, and alkaloids) in chromosomes, and the first plant **biosynthetic gene cluster** was identified in a study on the synthesis of the benzoxazinoid **DIMBOA** in maize (*Zea mays*) (reviewed in [61]). Benzoxazinoids are also synthesized in other Poaceae species such as wheat (*Triticum aestivum*), rye (*Secale cereale*), and barnyardgrass [13,62]. It is possible that the clustering of genes encoding protein complexes could be a means to provide optimal proportions of gene products and coordinate the regulation of the component genes; moreover, clustering of pathways could help to minimize self-toxicity as the intermediate compounds accumulate. Co-inheritance of whole pathways contributes to the possibility of similar modes of regulation of gene expression and accelerates response to changes in local environmental conditions, which would enhance plant survival [61,63]. In recent years several gene clusters encoding new secondary metabolites or collinear homologs have been identified in several plant species [13,63–70], suggesting that such gene clusters are more common in plant genomes than was initially believed. To date, ~30 examples of clusters of genes encoding products important for secondary metabolic pathways have been reported in plants (Table 2). A state-of-the-art approach (<http://plantismash.secondarymetabolites.org/precac/>) based on coexpression and related functions of a group of closely linked non-homologous genes typically resulted in estimates of 30–60 gene clusters in a single plant genome [71]. Similarly, 99 clusters were predicted to occur in the current draft genome of *E. crus-galli* [13], suggesting that more gene clusters are present in this weed.

Chemical Arms Race between Rice and Barnyardgrass

Although numerous studies of plant allelopathy have been undertaken, allelopathy between rice and barnyardgrass is among the most deeply examined because both the crop and weed genomes are readily available. As such, we describe the mechanism underlying the allelopathic interactions between rice and barnyardgrass as an example of a typical crop weed allelopathic interaction. In the rice–barnyardgrass coculture system, rice responds to barnyardgrass stress by increasing the production of putative allelochemicals, such as phenolic acids, momilactones, and flavones and their aglycones, and subsequently increasing allelopathic activity toward target weeds [72–74]. Although the specific chemical composition of the primary rice allelochemicals against barnyardgrass is still disputed, the molecular mechanisms regulating the biosynthesis of phenolic acids [74–77] and momilactones [78] are well documented. Kato-Noguchi and Peters [78] demonstrated that diterpenoid momilactones (especially momilactone B) from rice root exudations serve as crucial rice allelochemicals against barnyardgrass. A dedicated momilactone gene cluster has been identified as the genomic mechanism underlying the biosynthesis of this allelochemical [78,79] (Figure 2). In

Table 2. Characterized Gene Clusters for Biosynthesis of Specialized Metabolites in Plants

Chemical type	Chemical compound	Species	Genes in the cluster	Cluster function	Refs
Diterpene	Momilactone A	<i>Oryza sativa</i>	MAS, CYP99A2, CYP99A3, CPS4, KSL4	Inhibits the growth of rice weeds; defense system against pathogens and insects	[113]
Diterpene	Momilactone A	<i>Oryza punctata</i>	CPS4, CYP99A3, MAS, KSL4, CYP99A2	Pathogen defense	[67]
Diterpene	Momilactone A	<i>Echinochloa crus-galli</i>	CPS4, MAS, KSL4, CYP99A2	Defense system against pathogens and insects	[13]
Diterpene	Phytocassanes A–E	<i>Oryza sativa</i>	CPS2, KSL7, CYP71Z7, CYP76M7, CYP76M8	Pathogen defense	[114]
Diterpene	Phytocassanes A–E	<i>Leersia perrieri</i>	CPS2, KSL5, KSL7, CYP76M, CYP71Z	Pathogen defense	[67]
Diterpene	Oryzalde A	<i>Oryza sativa</i>	CPS2, KSL6, CYP71Z6, CYP76M8	Pathogen defense	[114]
Diterpene	Casbene diterpenoid	<i>Ricinus communis</i>	CYP726A13, SDR, CYP726A14, TPS-aNCS, CYP726A15, CYP726A16, AT, CYP726A17, TPS-aCS, CYP726A18, TPS-aCS, SDR, CYP726Ap, TPS-g, CYP80C9, CYP80C8	Pathogen and insect defense	[66]
Diterpene	Tirucalla-7, 24-dien-3 β -ol	<i>Arabidopsis thaliana</i>	CYP716A1, CYP716A2, PEN3, SCP-L1	Pathogen and insect defense	[66]
Diterpene	Cucurbitadienol	<i>Cucumis sativus</i>	CYP81Q58, CYP89A140, CYP81Q59, CPQ, BAHDACT, CYP87D19	Pathogen and insect defense	[66]
Terpene	–	<i>Solanum lycopersicum</i>	TPS21, CPT2, TPS20, TPS19, CPT1, TPS41, TPS18	Pathogen and insect defense	[115]
Terpene	–	<i>Solanum pimpinellifolium</i>	TPS21, CPT2, TPS20, TPS19, CPT1, TPS41, TPS18	Pathogen and insect defense	[116]
Triterpene	AvenacinA-1	<i>Avena strigosa</i>	SAD9, SAD10, SAD7, SAD1, SAD2	Defense against fungal pathogens	[117]
Triterpene	Marneral	<i>Arabidopsis thaliana</i>	CYP705A12, MRO, MRN1	Defense	[118]
Triterpene	Thalianol	<i>Arabidopsis thaliana</i>	ACT, THAD, THAH, THAS	Pest and disease defense	[119]
Triterpene	Cucurbitacin	<i>Cucumis sativus</i>	Csa6G088160, Csa6G088170, Csa6G088180, Bi, Csa6G088700, Csa6G088710	Cucumber bitterness formation	[65]
Triterpene	Lupeol	<i>Lotus japonicus</i>	AMY2, CYP71D353, CYP88D5	Potent antioxidant and anti-inflammatory agent	[64]
Benzoxazinoid	DIMBOA	<i>Zea mays</i>	Bx1–Bx5, Bx8	Herbivore and pathogen defense	[120]
Benzoxazinoid	DIMBOA	<i>Echinochloa crus-galli</i>	Bx1–Bx5, EcBx8	Allelopathy against rice	[13]
Cyanogenic glycoside	Linamarin/ lotaustralin	<i>Lotus japonicus</i>	CYP79D3/D4, CYP736A2, UGT85K2/3	Insect and herbivore defense	[121]
Cyanogenic glycoside	Cyanogenic glucoside	<i>Trifolium repens</i>	CYP79D15, CYP736A187, UGT85K17	Insect and herbivore defense	[63]
Cyanogenic glycoside	Linamarin/ lotaustralin	<i>Manihot esculenta</i>	CYP79D2, CYP71E7, UGT85K4/5	Insect and herbivore defense	[121]
Cyanogenic glycoside	Dhurrin	<i>Sorghum bicolor</i>	CYP79A1, CYP71E1, UGT85B1	Insect and herbivore defense	[121]

Table 2. (continued)

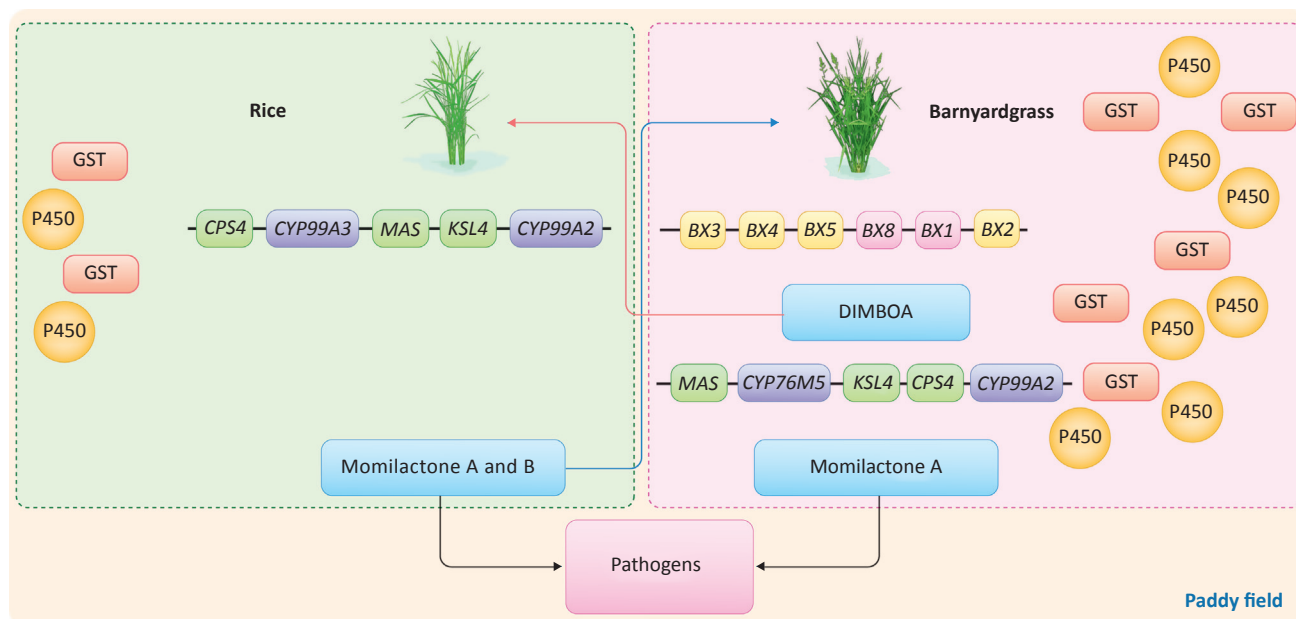
Chemical type	Chemical compound	Species	Genes in the cluster	Cluster function	Refs
Alkaloid	Noscapine	<i>Papaver somniferum</i>	PSSDR1, PSCXE1, CYP82X1, CYP8X2, PSAT1, PSMT2, CYP82Y1, PSMT3, CYP719A21, PSMT1	Antitussive and anticancer agent	[122]
Alkaloid	α -Tomatine	<i>Solanum lycopersicum</i>	GAME2, GAME11, GAME6, GAME17, GAME1, GAME18, GAME14, GAME4, GAME12, GAME8, GAME7	Defense against fungal, microbial, insect, and herbivoral attack	[123]
Alkaloid	α -Solanine	<i>Solanum tuberosum</i>	SGT3, GAME11, GAME6, SGT1, GAME12, GAME4, GAME8, GAME7	Defense against insects, disease, and herbivores	[123]
Alkaloid	α -Chaconine	<i>Solanum tuberosum</i>	SGT3, GAME11, GAME6, GAME12, GAME4, GAME8, GAME7	Defense against insects, disease, and herbivores	[123]
Polyketide	β -Diketone	<i>Triticum dicoccoides</i>	DMP, DMH, DMC, WES, CYP96B30	Defense	[124]
Polyketide	β -Diketone	<i>Hordeum vulgare</i>	CER-C, CER-Q, CER-U	Defense	[125]

addition, it has been reported that momilactone A in rice stems and leaves plays a major role in rice defense against fungal pathogens [80].

Intensive studies on the allelopathic effects of rice toward barnyardgrass have raised questions concerning whether and how barnyardgrass can in turn inhibit rice via allelopathy. Fang *et al.* [81] reported that **microRNAs** (miRNAs) are likely to play important roles in barnyardgrass response to rice allelopathy, and proposed that secondary metabolites released from allelopathic rice can recruit *Myxococcus* sp. myxobacteria. Moreover, the authors suggest that these species reciprocally increased the expression of barnyardgrass miRNAs, leading to inhibition of plant hormone signal transduction, such as p53 signaling pathways, in the weed. The genome of the hexaploid barnyardgrass species *E. crus-galli* was found to contain a total of 917 **cytochrome P450** (CYP) and 277 **glutathione S-transferase** (GST) genes, a significantly higher number than occurs in the genomes of other grasses or *Arabidopsis* [13]. These genes may enhance the detoxification capability of barnyardgrass [47]. Transcriptomic analyses indicate that genes involved in pathways associated with ‘cytochrome P450’, ‘brassinosteroid hormone metabolism’, and ‘phenylpropanoid metabolism’ were enriched and upregulated when barnyardgrass was cocultured with rice. Interestingly, three copies of the DIMBOA synthesis gene cluster were found in the *E. crus-galli* genome, and displayed perfect synteny with the maize genomic segment containing *BX1–BX5* and *BX8* [13]. Further experimental validation suggests that the biosynthesis of DIMBOA by barnyardgrass likely plays a key role in competitive interactions with rice (Figure 2). In addition, a gene cluster for momilactone A synthesis was also found in the barnyardgrass genome [13], and gene expression of this cluster dramatically increased following *Pyricularia oryzae* infection, indicating that its product, momilactone A, possibly also contributes to resistance to blast-infection resistance in *E. crus-galli* cocultured with rice. However, it is still not known how the weed *E. crus-galli* evolved gene clusters that greatly resemble those of the two biggest staple crops (maize and rice), highlighting the need for further research on the evolution of weediness, weed adaptations, and crop–weed interactions.

Crop–Parasitic Weed Interactions

Parasitic plants that interact with crops pose severe constraints to agricultural production, among which are the well-known parasitic genera *Striga* (witchweed), *Orobanche* (broomrape),



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Figure 2. Model of Rice–Barnyardgrass Interactions in a Paddy Field. Different allelochemicals (DIMBOA, momilactone A and B) that inhibit growth and development are biosynthesized by two gene clusters in rice and barnyardgrass, respectively, and both plants use the same secondary metabolite (momilactone A) for defense against field pathogens. In the rice genome, the gene cluster consists of five genes (three non-CYP genes: *KSL4*, *CPS4*, and *MAS*; and two CYP genes: *CYP99A2–3*) for the biosynthesis of momilactone A; in the barnyardgrass genome, two gene clusters, one consisting of six genes (two non-CYP genes: *BX1* and *BX8*; and four CYP genes: *BX2* and *BX3–BX5*) for DIMBOA synthesis, and another cluster consisting of genes (*KSL4*, *CPS4*, and *MAS*; and two CYP genes: *CYP99A2* and *CYP76M5*) for momilactone A synthesis. In addition, barnyardgrass has more genes encoding detoxification-related enzymes (CYPs and GSTs) than does rice. Abbreviations: CYP/P450, cytochrome P450 mono-oxygenase; DIMBOA, 2,4-dihydroxy-1,4-benzoxazin-3-one; GST, glutathione S-transferase.

and *Cuscuta* (dodder). All three genera have evolved similar parasitic characteristics, including host plant recognition, invasive haustoria formation, and regulation of the transfer of nutrients and other molecules between host and parasite [82]. We review below recent studies on the mechanisms underlying crop–parasitic weed interactions, with a focus on genetic exchanges between the two groups.

The haustorium – generally regarded as ‘the essence of parasitism’ – is used by parasitic plants in a wide range of behaviors including host attachment, host invasion, host-immunity avoidance, and nutrient transfer [83]. This specialized organ is not only used in the transfer of water and nutrients but also facilitates the bidirectional movement of macromolecules including proteins [84], metabolites [85], signaling molecules [86], mRNAs [87], and even miRNAs [88]. Kim *et al.* [87] demonstrated that parasitic plants are capable of exchanging extensive amounts of their transcriptomes with host plants, an indication of potential RNA-based interactions between parasite and host species. The authors further speculated that this exchange of mRNAs might help the parasite to track the physiological status of the host, and thereby facilitate parasitism.

New research provides the first clear evidence that macromolecule exchange can have functional consequences [88]. The authors of this study found that some novel dodder miRNAs of ~22 nt in length can be transferred via haustoria to the connected host stem regions, and specifically target

and significantly repress the expression of host genes (*TIR1*, *BIK1*, *SEOR1*, *AFB2*, and *AFB3*) involved in the plant stress defense system. Notably, the miRNA target sequence regions of these gene transcripts are conserved across a wide variety of plants, and this may account for the broad host range of dodder. This finding indicates that genetic editing of host plant miRNA target sites could be used to prevent miRNA binding to and silencing these mRNAs.

Horizontal gene transfer (HGT) of genes in both the plastid and nuclear genomes appears to be much more common in parasitic plants than in other angiosperms [89–91], possibly owing to frequent exchange of mRNA between parasites and hosts. In contrast to the findings for RNA transfer, where most research has focused on transfer from the parasite to the host, most studies examining HGT events have concentrated on parasitic plant genomes. *Striga hermonthica*, for example, was found to have obtained a functionally unknown gene from its natural hosts, sorghum and related species [92]. The first two parasitic plant genomes (*Cuscuta campestris* [14] and *C. australis* [15]) have been published, and in both cases it was found that genes in important pathways such as photosynthesis and nutrient uptake are absent from these dodders; in addition, Vogel *et al.* [14] identified 64 novel high-confidence HGTs from at least 32 different donor sequences. However, the functional significance of the HGT genes remains unknown, although enrichment analyses indicate a functional bias toward defense responses. The elevated expression of some of these genes in early developing haustoria suggested that they are potentially involved in the infection process [14], but further research will be necessary to verify this premise.

The salicylic acid (SA) and jasmonic acid (JA) signaling pathways play essential roles in the activation of host resistance measures to parasitic plants [93,94], and there is some evidence that the ABA pathway may also play a role in host defense responses to parasitic plants [95]. Cloning of the first resistance gene in cowpea (*Vigna unguiculata*) conferring resistance to witchweed (*Striga gesnerioides*) led to the identification of a predicted coiled-coil nucleotide-binding site leucine-rich repeat (CC-NBS-LRR) resistance protein (R gene) [96], implying that the host plants rely on similar molecular mechanisms for defense against plant parasitism and microbial pathogenicity. *WRKY45* in rice can modulate crosstalk in the resistance of rice against *Striga hermonthica* by positively regulating both the SA and JA pathways [97], and Gobena *et al.* [98] reported that functional loss of the *LOW GERMINATION STIMULANT 1* (*LGS1*) gene in barley could change the type of strigolactone from a highly active *Striga* germination stimulant to a less active derivative, which may be useful in the breeding of crops with improved *Striga* resistance at earlier stages.

Concluding Remarks and Future Perspectives

To date, research at the whole-genome scale has focused on a small number of agricultural weed species. For weedy crop relatives, the availability of related crop genomes is a great advantage and investigations can be performed using reference mapping-based approaches. However, limitations remain because the crucial genetic basis of weediness may hide in highly divergent or specific genomic regions. Therefore, pan-genome-based investigations may be necessary to identify key genetic determinants in weedy crop relatives. However, for weedy non-crop relatives the currently assembled genomes are very fragmented and contain numerous gaps, and none has been assembled into chromosomes, which greatly impedes accurate and in-depth evolutionary investigations into their adaptations. The small number of weed genomes and their inferior assembly quality could reflect the complex nature of weed genomes (e.g., high polyploidy, heterozygosity, large genome size) and their taxons. In addition, large populations of non-crop-relative weeds are rarely established, preventing the construction of high-resolution genetic linkage maps. However, we believe that these issues could be solved in the near future using state-of-the-art sequencing (e.g., single-molecule sequencing, Hi-C, BioNano, 10× Genomics) and bioinformatic approaches. In

Outstanding Questions

Does a common molecular mechanism underlie crop de-domestication?

Why does the de-domestication process occur more frequently in some crops than in others?

Is DIMBOA tolerance the genetic basis for the higher allelopathic ability of rice varieties?

How did biosynthetic gene clusters for allelopathy assemble in different crop/weed genomes? Do they derive from common ancestors or did they arise through parallel evolution?

Is genetic crosstalk also an important form of interaction among non-parasitic weeds (such as barnyardgrass)?

addition to large genomic efforts, integrated investigations based on multi-omics should be performed to better understand the genetic basis of weediness.

Sustainable and environmentally friendly agriculture aims to reduce the use of chemical herbicides without compromising crop yield and food quality. One strategy is to develop competitive crop cultivars via breeding using our understanding of the mechanisms underlying crop–weed interactions. Unlike crops, the distribution of agricultural weeds is unpredictable. Thus, it would be challenging to directly edit weed genomes to make all weed populations less invasive. However, it could be feasible to breed crops that are more competitive. For example, taking advantage of what we know about allelopathic interactions between rice and barnyardgrass, rice cultivars with improved DIMBOA resistance could be bred in the near future. In addition, the biosynthesis of momilactones and other allelochemicals could be improved by metabolic engineering approaches to better protect crops against weeds. Moreover, knowledge of genetic element exchange during crop and parasitic plant interactions would guide genome editing at sites targeted by genetic elements transferred from parasites, and thereby facilitate breeding of crop varieties with reduced parasite infections.

The adaptation of weedy crop and non-crop relatives not only poses a threat to the global food supply but also provides a unique view into the process of plant evolution. In this review we cover major evolutionary innovations of these two categories of agricultural weeds as well as crop–weed interactions, and we believe this knowledge will make a major impact on weed management and crop improvement in agroecosystems (see Outstanding Questions).

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