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COMPREHENSIVE REVIEW

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Defense heterosis as a novel plant protection strategy: From theory to breeding practice

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Abstract

Plant diseases cause severe yield losses annually, threatening global food security. Traditional resistance breeding faces challenges such as rapid pathogen evolution and yield-defense trade-offs. Defense heterosis—the phenomenon where F_1 hybrids derived from crosses between genetically distinct parental lines exhibit superior disease resistance compared to parents—provides a promising solution. This review summarizes recent advances in understanding defense heterosis, from its conceptual evolution to modern genomic insights. Here, we outline three classical genetic hypotheses (dominance, overdominance, and epistasis) and introduce molecular mechanisms, including differentially expressed genes, epigenetic regulation (DNA methylation, histone modifications), and salicylic acid-mediated coordination of immunity. Case studies across rice, maize, wheat, and potato demonstrate the prevalence and variability of defense heterosis. We highlight that future efforts should utilize multiomics data, genome editing, and microbiome manipulation to predict and deploy defense heterosis. This integrated perspective bridges fundamental research and agricultural applications, offering a roadmap to enhance crop resilience and food security.

KEYWORDS

crop breeding, defense heterosis, disease resistance, genetic mechanisms, hybrid vigor, molecular regulation

1 | INTRODUCTION

Plant diseases represent a major threat to global food security, causing approximately 30% of annual crop production losses worldwide.[1] Conventional breeding for disease resistance primarily relies on gene introgression.[2] However, this approach often encounters challenges including rapid breakdown of resistance, long breeding cycles, and the persistent difficulty of balancing high yield with durable resistance.[3] Researchers have discovered that plant hybrids exhibit enhanced disease resistance compared to their parent lines, a phenomenon termed "defense heterosis."[4] This phenomenon establishes a new paradigm for simultaneously achieving enhanced productivity and improved disease resistance in crops.

Accumulating evidence indicates that defense heterosis is widespread in major crops such as rice,[5,6] maize,[7–10] wheat,[11,12] and potato.[13] At the genetic level, it involves dominance and other mechanisms, whereas at the molecular level, it encompasses differentially expressed genes (DEGs),[11,14] epigenetic regulation,[15,16] and hormone signaling networks.[4,17,18] Nevertheless, the mechanisms underlying defense heterosis remain complex and vary among different crop–pathogen interaction systems. In addition, the relationship between defense and yield heterosis remains poorly understood.

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This review systematically synthesizes historical developments and recent advances in defense heterosis research, dissecting its genetic and molecular mechanisms, summarizing representative case studies across diverse crop species, and discussing possible applications in crop breeding.

2 | CONCEPTUAL EVOLUTION OF DEFENSE HETEROSIS

As an integral component of heterosis, defense heterosis is conceptualized in light of the evolutionary trajectory of this classical phenomenon. We will first outline the origins of hybrid vigor and heterosis, followed by a discussion of the rationale behind the proposal of the concept of "defense heterosis."

2.1 | Early observations of hybrid vigor

As early as 544 AD, the Chinese agricultural book *Qimin Yaoshu* documented that mules created by crossing horses and donkeys were significantly larger than both parents; later veterinary studies also confirmed that mules possess greater disease-resistant advantages compared to horses.[19] In 1766, the German botanist Kölreuter reported growth vigor in interspecific plant hybrids such as tobacco, carnations, and *Datura*.[20] A century later, the founder of modern genetics, Mendel, systematically recorded in his famous pea hybridization experiments that F_1 hybrids commonly exhibited longer stems than their parents.[21] During the same period, Darwin also paid close attention to this hybrid superiority phenomenon. In his book *The Effects of Cross and Self Fertilisation in the Vegetable Kingdom*, he conducted quantitative analyses of hybrid performance in multiple species, providing crucial data records (Figure 1).[22] These observations, spanning multiple species and centuries, laid the groundwork for understanding the performance enhancements conferred by hybridization.

2.2 | Proposal and definition of "heterosis"

As hybrid vigor became increasingly documented in the early 20th century, plant breeders sought to reconcile these observations with Mendelian inheritance. In 1914, Shull, demonstrated that two independent, nonallelic genes redundantly determine the triangular capsule shape in shepherd's purse (*Capsella bursa-pastoris*). Importantly, he argued that the superior performance of hybrids does not necessarily arise from heterozygosity per se.[23] To avoid the ambiguity inherent in terms such as "heterozygotic stimulation" or "the stimulating effects of hybridity," Shull coined the term "heterosis," a neutral designation for the phenomenon where F_1 hybrids outperform their parents in specific traits.[23,24] By decoupling physiological vigor from its underlying genetic basis, "heterosis" emphasizes the phenotypic outcome without presuming a singular genetic mechanism.

Shull also synthesized contemporary reports on hybrid superiority and noted that hybrids consistently outperformed their parents not only in growth vigor but also in disease resistance and general stress tolerance.[23] Consequently, he argued that the term "heterosis," in contrast to its synonym "hybrid vigor," considerably broadened the scope of traits encompassed by hybrid advantage. It is not limited to visibly enhanced vitality such as increased yield or biomass but also includes any superior performance exhibited by F_1 hybrids under specific environmental stresses or biotic challenges. Thus, Shull defined heterosis as "the interpretation of increased vigor, size, fruitfulness, speed of development, resistance to disease and to insect pests, or to climatic rigors of any kind, manifested by crossbred organisms as compared with corresponding inbreds, as the specific results of unlikeness in the constitutions of the uniting parental gametes (Figure 1)."[25] In this review, we will use "heterosis" as a generalized term to describe such phenomena while still adopting "hybrid vigor" to characterize the biomass and yield heterosis.

2.3 | Emergence of defense heterosis

To address the severe challenge of plant diseases and meet the growing food demand, plant breeders have long been dedicated to developing resistant cultivars through hybridization. Early explorations in this field date back to 1869, when the British horticulturist James Clark serendipitously developed Magnum Bonum, a hybrid offspring of the potato cultivars "Early Rose" and "Paterson's Victoria." He observed that this hybrid not only exhibited significant resistance to the devastating potato late blight (caused by *Phytophthora infestans*) but also maintained a high yield level.[26] Subsequently, in 1909, Nilsson-Ehle systematically documented hybridization data for resistance to wheat yellow rust (caused by *Puccinia striiformis*), clearly demonstrating that progeny in several hybrid combinations exhibited superior resistance to yellow rust compared to their parents.[12]

Following these observations, further research confirmed that the phenomenon of hybrid progeny outperforming their parents in disease resistance was prevalent across diverse species.[8,11,13,27,28] However, the terms used to describe this phenomenon, such as "hybrid vigor in disease resistance"[25] or "heterosis in disease resistance,"[28] were varied and lacked

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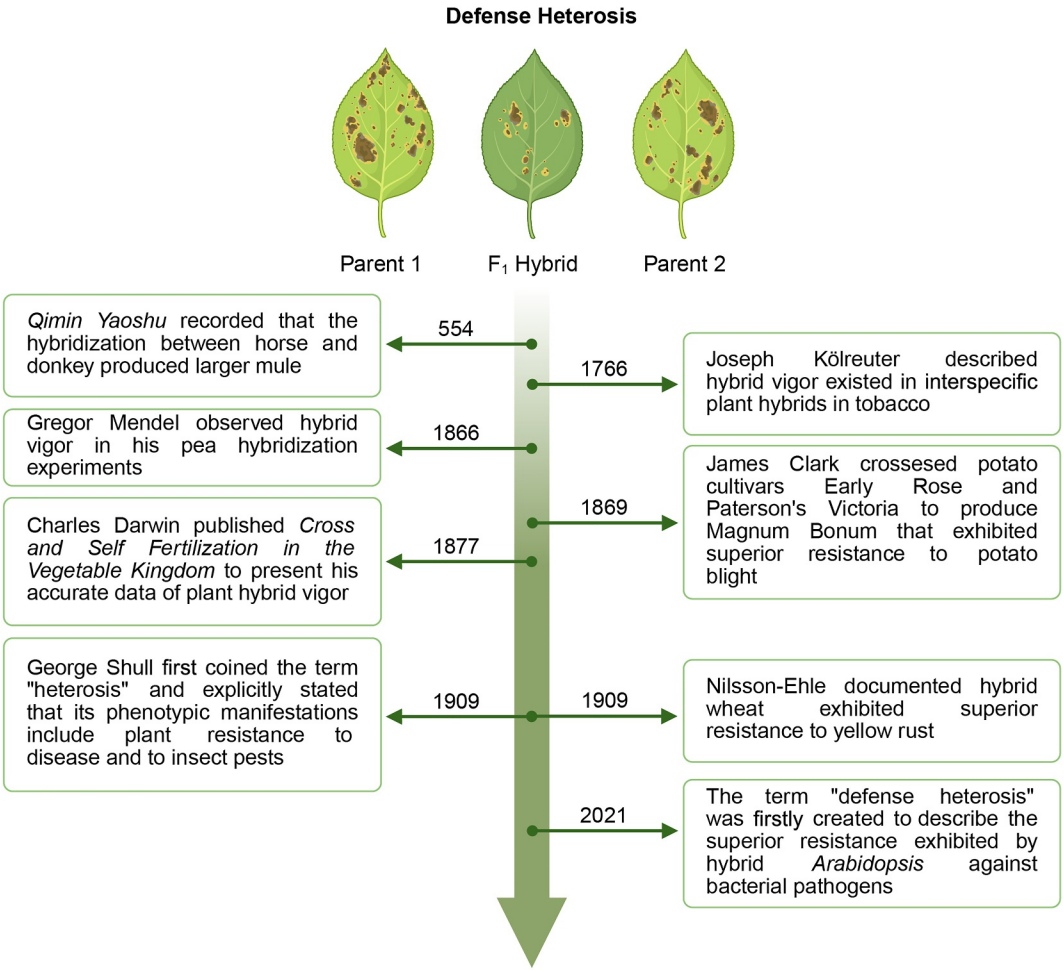

FIGURE 1 Historical timeline of the conceptual development of defense heterosis. The phenomenon of hybrid vigor was observed and utilized in early agricultural practices. With advancing research on hybrid vigor, the concept of "heterosis" was formally coined to denote the superior performance of hybrid offspring over their parents in diverse traits. As an integral component of heterosis, "defense heterosis" subsequently gained attention and has gradually emerged as a distinct field of research. The image was created with BioRender.com, with permission.

uniformity. This terminological inconsistency significantly hindered information retrieval and systematic research on defense heterosis, reflecting the then-prevailing perception that it was merely a secondary byproduct of general heterosis.

This changed markedly in 2021, when a study on *Arabidopsis thaliana* formally coined the term "defense heterosis" to describe the enhanced resistance observed in hybrid progeny against bacterial pathogens.[4] By preserving the conceptual neutrality of "heterosis" while explicitly focusing on defense pathways, the term precisely captures the heterosis linked to biotic stress resistance (e.g., to microbes and insect pests). Its introduction highlighted the need in plant protection science for a dedicated framework to study heterosis in immunity. Consequently, "defense heterosis" emerged as a distinct research field, driving efforts to unravel its universal principles and core mechanisms.

3 | GENETIC MECHANISMS OF DEFENSE HETEROSIS

To explain the genetic basis of heterosis, three prevailing hypotheses have been proposed: the dominance hypothesis, the overdominance hypothesis, and the epistasis hypothesis.[29] Using these three perspectives and integrating relevant data, we will dissect the genetic mechanisms underlying defense heterosis.

3.1 | Dominance hypothesis

In 1910, Bruce developed a mathematical model based on Mendel's law of random segregation, proposing the dominance hypothesis to explain hybrid vigor.[30] This hypothesis was subsequently refined by Jones.[31] The core premise of the dominance hypothesis is that

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during hybridization, a dominant favorable allele from one parent masks a recessive deleterious allele from the other parent. This allows the F_1 hybrid to accumulate favorable dominant alleles from both parents. Consequently, the proportion of advantageous traits increases in the hybrids, whereas the expression of disadvantageous traits decreases, resulting in heterosis (Figure 2).

Subsequent genetic studies across various crops, including peas,[32] rice,[33] maize,[34] and sorghum,[35] have consistently demonstrated that the dominance effect is a significant mechanism driving hybrid vigor. In terms of defense heterosis, several studies have employed Griffing's diallel analysis to investigate defense heterosis against different pathogens in maize.[7–10] These studies show that crosses between two resistant inbred lines typically produce F_1 progeny with superior disease resistance compared to their parents. These observations align strongly with the predictions of the dominance hypothesis: resistance-associated favorable alleles that exhibit dominance are complemented and accumulated in the F_1 hybrids.

However, studies have also revealed that some hybrid combinations involving susceptible parents produce progeny displaying enhanced resistance.[9,13] This indicates that although dominance complementarity is a primary mechanism explaining defense heterosis, other genetic mechanisms also play crucial roles. Together, these mechanisms constitute the complex genetic foundation underlying defense heterosis.

3.2 | Overdominance hypothesis

The overdominance hypothesis offers an alternative explanation for the genetic mechanism of heterosis.[36,37] This hypothesis posits that the alleles governing heterosis exist in a heterozygous state in hybrids, and this heterozygous state contributes more significantly to the phenotype than the homozygous state.

Although quantitative genetic studies suggest that overdominance effects contribute relatively less to heterosis than dominance effects,[38,39] their existence has been firmly substantiated by concrete evidence.

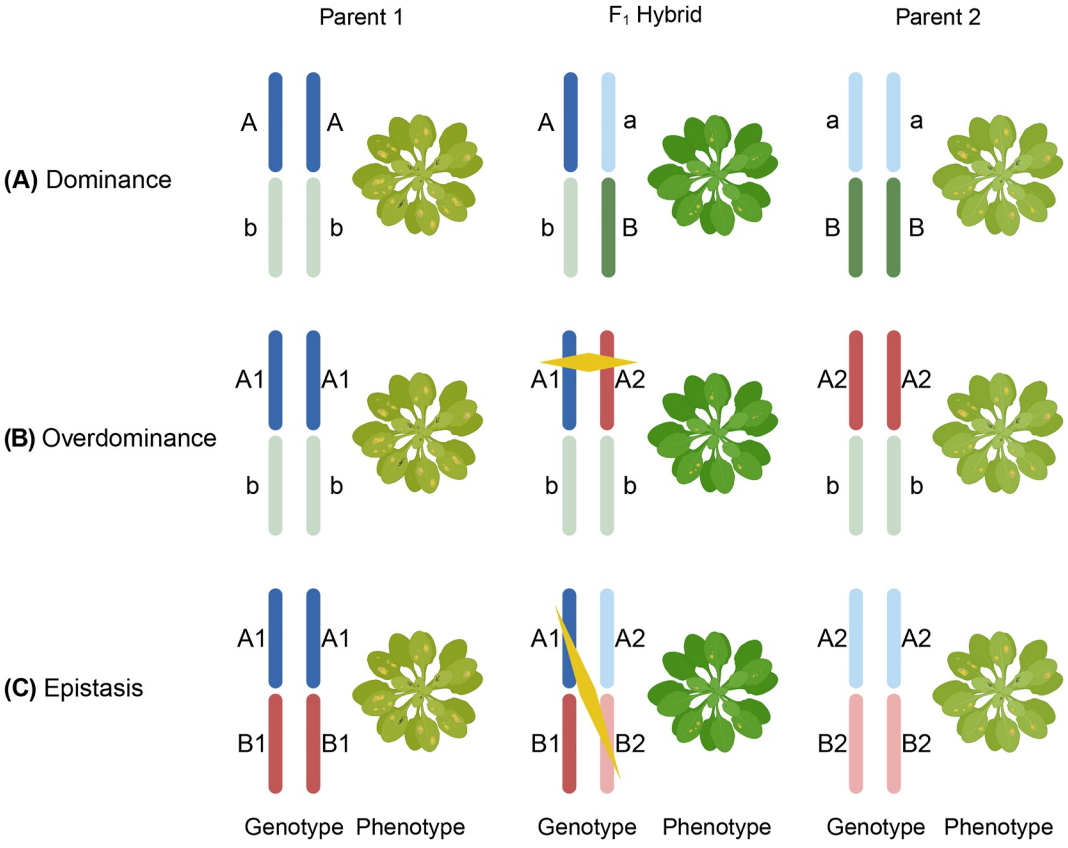

FIGURE 2 Schematic illustration of the three major genetic hypotheses governing defense heterosis. (A) Dominance hypothesis: favorable dominant alleles for defense mask deleterious recessive alleles, which accumulate in the hybrid progeny. (B) Overdominance hypothesis: the heterozygous state at specific loci confers superior phenotypic effects on defense heterosis when compared to either homozygous state. (C) Epistasis hypothesis: epistatic interactions between nonallelic genes contribute to the formation of defense heterosis. The image was created with BioRender.com, with permission.

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For example, heterozygous alleles *FNS* (flavone synthase) confer flower color heterosis to the hybrid of *Mimulus lewisii*.[40] The F_1 hybrid from crossing the tomato inbred line M82 with its *sft* mutant gains a 60% yield heterosis solely due to a heterozygous pair of *SFT* (single flower truss) genes.[41] The oil palm (*Elaeis guineensis*) hybrid variety *tenera* also possesses a heterozygous pair of *SHELL* genes, conferring the characteristic of thin-shelled, oil-rich fruit and boosting its yield by 30% relative to its parents.[42]

Currently, documented cases of overdominance affecting defense heterosis remain limited. Genome-wide association studies (GWAS) offer a powerful approach for identifying such genetic loci. By linking high-density single nucleotide polymorphism (SNP) markers with phenotypic data, GWAS significantly narrows down genomic regions harboring candidate genes associated with defense heterosis.[33,43] However, this method alone cannot reliably distinguish true overdominance effects from those caused by closely linked dominant loci.[44,45] Therefore, it is essential not only to validate the contributions of heterozygous candidate loci to defense heterosis through genetic approaches but also to elucidate how the corresponding genetic elements function in a heterozygous state at the molecular level. If key genes governing defense heterosis via overdominance can be identified, it may become feasible to introduce heterozygous favorable resistance alleles into high-yield hybrid crops using precise gene-editing technologies.[46]

3.3 | Epistasis hypothesis

In 1907, Bateson proposed the concept of epistasis and experimentally revealed the genetic mechanism of nonallelic gene interactions.[47] Minvielle analyzed a two-locus model and found that, even without dominance, interactions between genes at different loci can cause some hybrid offspring to surpass parents, thus generating heterosis (Figure 2).[48] Subsequently, multiple studies found that epistatic effects play a regulatory role in the formation of heterosis in crops such as rice,[49] wheat,[50] and maize,[51] supporting the inclusion of the epistasis hypothesis as one of the three classical genetic hypotheses for heterosis.

The three aforementioned studies all utilized GWAS to demonstrate the roles of epistasis in the formation of heterosis, reflecting the natural advantages of GWAS in dissecting epistatic loci. Specifically speaking, to test all possible SNP–SNP interactions, the square of the number of high-density SNPs would lead to an astronomical computational burden. However, GWAS first identifies loci with significant additive effects to delineate a smaller range of candidate SNPs, thereby significantly reducing the computational load. Nevertheless, this approach may miss certain important loci that exhibit nonsignificant additive effects but have significant interaction effects.[52] Therefore, functional genomics methods that do not rely solely on direct genetic mapping can serve as a complementary strategy.[53] Functional genomics infers epistatic networks through expression quantitative trait locus (eQTL) mapping. The core idea is to treat gene expression levels as molecular phenotypes and to search for their regulatory loci across the genome. When the regulatory effect of a distant locus (a *trans*-eQTL) on the expression of a target gene significantly depends on the genotypic background of another locus, an epistatic interaction (eQTL × eQTL interaction) is detected. By systematically identifying such "context-dependent" regulatory relationships, it is possible to construct a system-level epistatic map that uses gene expression as an intermediate node to reveal how nonadditive genetic interactions reshape transcriptional networks.[54,55] This approach will ultimately elucidate the genetic basis of complex traits, such as defense heterosis, from a regulatory mechanism perspective.

4 | MOLECULAR MECHANISMS OF DEFENSE HETEROSIS

4.1 | The role of differentially expressed genes in defense heterosis

With the rapid development of high-throughput sequencing technologies, researchers have begun to elucidate the molecular mechanisms underlying heterosis from the perspective of gene expression levels. If the gene expression pattern of the hybrid differs from that of its parents, it may lead to phenotypic changes in the F_1 hybrids, consequently influencing the formation of heterosis. Differences in gene expression levels manifest in additive or nonadditive patterns.[56] The average expression level of alleles from both parents is termed the mid-parent value (MPV). When the expression level of a certain gene in the F_1 hybrid equals the MPV, it is classified as additive expression. Deviations from the MPV are termed nonadditive expression, which can be further categorized into four patterns,[57] including above high parent, high parent, low parent, and below low parent (Figure 3).

The regulatory role of DEGs in heterosis has been extensively documented in species such as *Arabidopsis*,[14] rice,[58–60] maize,[56,61–63] and wheat.[64] Although most studies focus on hybrids exhibiting biomass or yield heterosis, integrated analysis of transcriptomic data reveals that many defense-related genes exhibit a nonadditive repressed expression pattern.[14,56] This downregulation may attenuate defense responses, potentially explaining why many elite hybrid rice varieties display yield heterosis without concurrent enhancement in disease resistance.[65,66]

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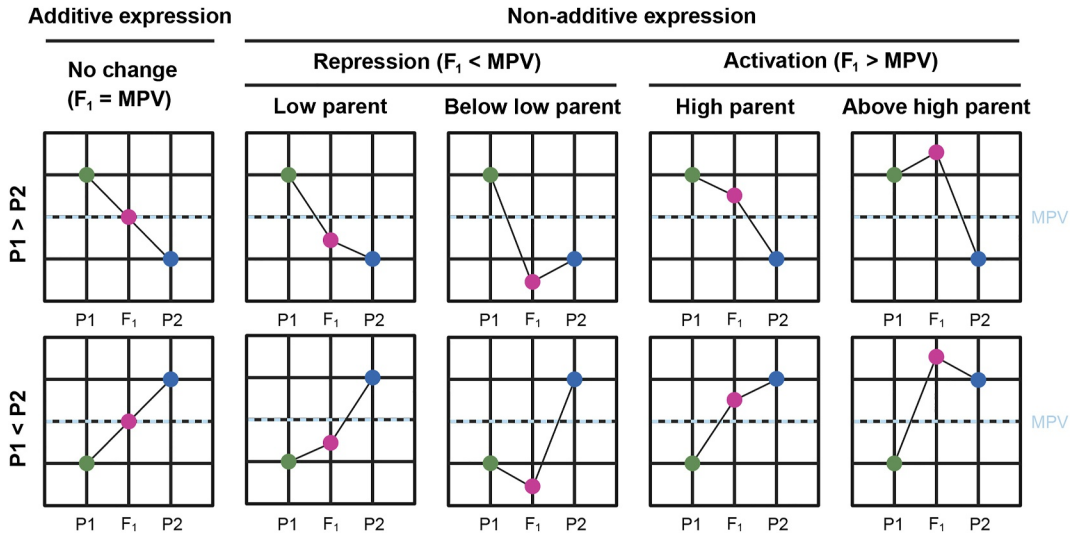

FIGURE 3 Types of gene expression patterns in the F_1 hybrid compared to its parents (P1 and P2). An additive expression pattern occurs when F_1 expression equals the MPV (average of parental allele expression), whereas deviation from the MPV indicates a nonadditive expression pattern, which is further classified into four patterns based on expression bias between the F_1 hybrid and parents, including low parent, below low parent, high parent, and above high parent. The image was created with BioRender.com, with permission. MPV, mid-parent value.

Regarding cases exhibiting defense heterosis, DEGs have indeed been demonstrated to contribute to its manifestation. A study demonstrated that in nascent allohexaploid wheat, certain immune-related genes show expression-level dominance (ELD) favoring the *Aegilops tauschii* allele, conferring superior powdery mildew resistance compared to its diploid progenitor.[11] Moreover, above-high-parent expression of salicylic acid (SA) biosynthesis genes in *Arabidopsis* F_1 hybrids is critical for bacterial defense heterosis.[17] Notably, the core circadian transcription factor circadian clock associated 1 (CCA1) coordinates growth and immunity genes to overexpress in an above-high-parent pattern rhythmically, enabling the F_1 hybrids to simultaneously achieve both biomass and defense heterosis.[4]

4.2 | Epigenetic mechanisms of defense heterosis

Epigenetics reveals that, atop the genetic information carried by the DNA sequence, there exists another heritable layer of information constituted by covalent modifications to DNA and associated histones.[67] This layer encodes regulatory instructions for gene expression, exhibits dynamic responsiveness to environmental changes, and can be stably transmitted during mitotic and meiotic cell divisions.[68]

In a 2010 study, Sunao and Kazuyoshi observed that potato hybrids exhibited strong hybrid vigor compared to their inbred lines and parental cultivars. Importantly, these hybrids also displayed significantly higher DNA methylation heterozygosity than the inbreds and parents, suggesting that DNA methylation modifications may serve as a key epigenetic mechanism regulating hybrid vigor.[69] Subsequent studies have revealed marked differences in DNA methylation between hybrids and their parents in *Arabidopsis*,[18,70–74] rice,[16,75] maize,[76,77] tomato,[78] Chinese cabbage,[79] and pigeonpea.[15] For defense-related genes, elevated methylation in hybrids leads to nonadditive repressive expression, thereby attenuating basal defense and facilitating biomass heterosis. Examples include the downregulated *PR1*/*PR2* in pigeonpea hybrids,[15] the suppressed *Xa1* in rice hybrids,[16] and the silenced *PAL* locus in tomato hybrids.[78]

Histone modifications represent another class of crucial chromatin marks that influence hybrid vigor. Similar to DNA methylation, histone methylation suppresses the expression of immunity-related genes, thereby maintaining a growth–defense balance in hybrids exhibiting hybrid vigor. For instance, in allohexaploid wheat, immunity-related genes such as *CERK1*, *PR1*, and members of the *WRKY* family have been demonstrated to be suppressed by the H3K27me3 modification.[80] In contrast, histone acetylation promotes defense heterosis. In *Arabidopsis* hybrids, histone H3 acetylation (H3Ac) levels are significantly enhanced at the promoter regions of key SA biosynthetic genes. This enhancement promotes SA synthesis, consequently conferring defense heterosis against bacterial pathogens.[17] Subsequent research further revealed that this H3Ac enhancement at SA biosynthetic gene loci is predominantly regulated by the core circadian oscillator, CCA1.[4] Moreover, the rhythmic expression of *CCA1* itself is dynamically regulated by

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H3Ac. The circadian H3Ac modification enables CCA1 to coordinate defense and biomass heterosis by a dual mechanism: promoting defense responses before dawn, and repressing its own activity during the day. The latter releases photosynthesis and metabolism-related genes from repression, thereby facilitating growth. In summary, epigenetic modifications play various yet crucial roles in regulating defense heterosis.

4.3 | SA regulation of defense heterosis

SA, a key plant immune hormone, plays a central role in coordinating both biomass and defense heterosis. A study revealed that in *Arabidopsis* hybrid combinations exhibiting typical biomass heterosis, the F_1 progeny universally display a low-parent pattern of SA biosynthetic gene expression levels and SA accumulation levels.[81] Notably, increasing SA content in F_1 plants through exogenous application or genetic editing techniques leads to the disappearance of their biomass heterosis.[18,81,82] In hybrid combinations that manifest defense heterosis, F_1 progeny accumulate SA to levels exceeding those of both parents after bacterial challenge, and this above-high-parent SA surge is indispensable for the observed resistance advantage, as blocking SA biosynthesis abolishes the defense heterosis.[17]

In brief, constitutively accumulated SA is detrimental to biomass heterosis, whereas pathogen-induced, timely, and above-high-parent accumulation of SA drives defense heterosis. *Arabidopsis* orchestrates this balance through chromatin remodeling by DDM1 (decreased DNA methylation 1), which locks the parental SA baseline into an optimal range,[18] and through the circadian regulator CCA1, which temporally regulates SA accumulation. CCA1 ensures that above-high-parent accumulation of SA occurs after pathogen infection or during the night, thereby avoiding interference with the above-high-parent expression of growth-related genes during the daytime.[4]

Notably, the SA-mediated defense heterosis may be further shaped by its crosstalk with other immune hormones, particularly jasmonic acid (JA). The interaction between SA and JA pathways is multifaceted. Although classical studies often highlight their antagonistic relationship—where SA suppresses JA biosynthesis and signaling,[83]—emerging evidence indicates that SA can also activate JA signaling via its receptors NPR3 and NPR4 in a noncanonical manner, thereby promoting effector-triggered immunity.[84] Supporting the relevance of this interaction in heterosis, studies in *Arabidopsis* hybrids show that blocking SA biosynthesis alters the expression of JA-responsive genes.[82] These findings position JA not only as a crucial component in SA-mediated immune regulation but also as a hormone that may independently contribute to defense heterosis.

5 | PHENOTYPIC DIVERSITY OF DEFENSE HETEROSIS

The observation of defense heterosis now extends beyond model systems to important crops, including rice, wheat, maize, potato, and pepper. Accordingly, although a significant portion of the research has focused on identifying optimal hybrid combinations and dissecting the phenotypic contributions of the three classical heterosis mechanisms through genetic analysis, other studies have begun to preliminarily uncover the underlying molecular mechanisms.

5.1 | Dominance effects and strategic pyramiding

The classical dominance hypothesis is frequently observed in the defense heterosis of maize. Systematic diallel studies on resistance to various pathogens have demonstrated that the strongest defense heterosis is often derived from crosses between two highly resistant parents.[8–10] For instance, the maize hybrid derived from crossing P2 × P7 displayed superior heterosis against *Exserohilum turcicum*,[10] underscoring the substantial contribution of dominance effects to defense heterosis. This pattern suggests that complementing dominant resistance alleles from both parents can effectively mask deleterious recessive alleles, leading to hybrid performance that surpasses the MPV.

Gene pyramiding can be viewed as a strategic prebreeding approach that maximizes the utilization of dominance effects. Accumulating multiple dominant R genes into a single parental line ensures that the resulting hybrids exhibit potent and broad-spectrum defense heterosis, fundamentally underpinned by the collective action of these dominant alleles. A prime example comes from rice breeding. Although many commercial rice hybrids with yield heterosis are often more susceptible than parents such as Dianheyou 80[65] or Liangyoupeiju,[85] researchers introduced the broad-spectrum blast resistance genes *Pi-1*, *Pi-9*, and *Pi-k^h* into the high-yield restorer line Fuhui 676 using backcross breeding combined with molecular marker-assisted selection.[86] This approach produced a new restorer line (line 6) with the three resistance genes and the genetic background of the original restorer line. F_1 hybrids derived from crosses between this line and male-sterile lines retained the high-yield characteristics and also exhibited strong blast resistance.

5.2 | Contributions of overdominance and epistasis

Genetic component analysis is a key statistical method in complex quantitative trait studies. It decomposes the

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genetic contributions to a trait into different components to reveal their relationships with the phenotype. According to classical heterosis theory, defense heterosis is associated with nonadditive genetic effects, such as overdominance and epistasis, which are key determinants of its magnitude. Maize, as the first crop to translate heterosis theory into industrialized practice,[87] has adopted standardized Griffing's diallel analysis[88] and the Gardner–Eberhart model[89] to dissect the genetic basis of heterosis. To counteract severe yield losses caused by disease, research teams from different continents have conducted systematic diallel studies of defense heterosis against four key pathogens: *E. turcicum* (northern leaf blight),[10] *Bipolaris maydis* (southern leaf blight),[8] *Colletotrichum sublineola* (anthracnose), and *Fusarium verticillioides* (*Fusarium* ear rot). These studies reveal that highly susceptible parents also confer significant defense heterosis to their progeny. For example, the F_1 hybrid of the susceptible varieties Mo19 and Va6 exhibited enhanced resistance against *B. maydis*.[8] This suggests that the dominance effect alone cannot fully explain the genetic mechanisms underlying defense heterosis. Instead, overdominance and epistasis are the primary genetic mechanisms driving this phenomenon of "susceptible parents contributing strong defense heterosis." Furthermore, the elite maize hybrids and parental lines identified by these studies provide a solid genetic foundation for future molecular dissection of defense heterosis and for molecular breeding.

Unlike the Griffing diallel cross, which evaluates all possible hybrid combinations in maize heterosis studies, the line × tester mating design assesses only selected parental crosses to estimate combining ability for heterosis, allowing superior hybrids to be identified more rapidly. This approach was adopted in two studies on defense heterosis, one in potato against *Alternaria solani*[13] and the other in pepper against chilli leaf curl virus.[27] Both revealed that specific combining ability effects were markedly stronger than general combining ability effects, indicating that defense heterosis arises primarily from gene interactions unique to particular crosses rather than from dominant effects inherent to the parents.

5.3 | Preliminary insights into molecular mechanisms

Beyond the dissection of genetic effects, preliminary molecular studies are beginning to reveal the mechanisms underpinning defense heterosis. Cui et al. systematically studied the disease resistance phenotypes of hybrid rice N6Y7075 inoculated with three strains of *Xanthomonas oryzae* pv. *oryzae* and 15 strains of *Magnaporthe oryzae*.[5] They found that N6Y7075 exhibited resistance to bacterial blight and rice blast that was superior to the male parent FH7075 and comparable to the female parent NX6A. Transcriptome analysis revealed that the expression levels of defense-related genes in N6Y7075 were significantly higher than those in the susceptible parent FH7075 and were similar to or higher than those in the resistant parent NX6A. Crucially, transcription factors such as WRKY45-1 were specifically activated in the hybrid N6Y7075. By regulating programmed cell death and defense gene expression, these transcription factors enhanced the efficiency of the defense signaling pathway, thereby promoting the formation of defense heterosis. This study offers new insights into the molecular mechanisms underlying heterosis in hybrid rice and preliminarily uncovers the potential roles of transcription factors in regulating defense heterosis.

Wheat, as an allohexaploid, can be regarded as an important crop with permanently fixed heterosis.[90] A study reported that nascent synthetic allohexaploid wheat also exhibits defense heterosis against powdery mildew when compared to its diploid progenitor *A. tauschii*.[11] This defense heterosis is underpinned by several molecular mechanisms mentioned above. Firstly, a significant fraction of resistance genes, including NBS-LRR and chitinase homologs, display ELD favoring the *A. tauschii* allele, leading to elevated immune responses. At the epigenetic level, miRNAs such as miR9009, miR167, and miR319 exhibit nonadditive repression, leading to derepression of their targets, including R gene analogs and stress-responsive transcription factors, thereby amplifying defense signaling. Collectively, these small RNA-driven and ELD-based regulatory circuits confer robust, heritable disease resistance in the nascent allohexaploid wheat.

6 | CONCLUSION AND FUTURE DIRECTION

Defense heterosis, like heterosis in other traits, has been demonstrated to be widespread across diverse plant species. A deeper dissection of its underlying genetic and molecular mechanisms will establish a solid theoretical foundation for the precise prediction and efficient utilization of this phenomenon in modern crop breeding.

Currently, genetic dissection of plant defense heterosis primarily relies on traditional combining ability analysis and phenotypic selection, which have relatively limited precision and struggle to pinpoint key genetic loci. Learning from successful research on yield heterosis,[33,43] future studies could utilize large-scale genome resequencing and multiomics data. Integrating technologies such as GWAS and expression eQTL mapping will enable systematic identification of defense-heterosis-associated loci, rare allelic variations, and their epistatic regulatory networks,

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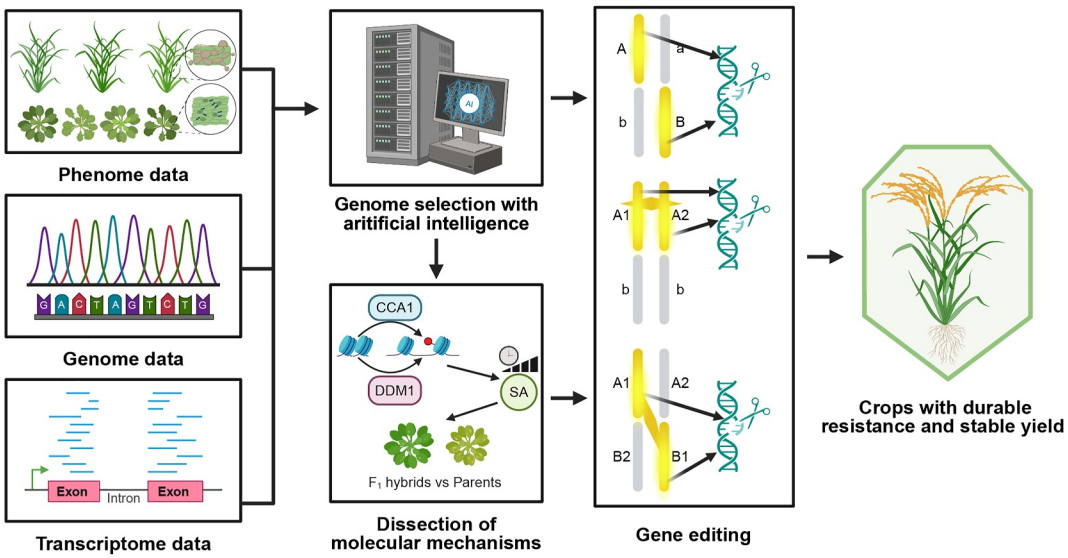

FIGURE 4 Framework for predicting and utilizing defense heterosis. This workflow initiates with the large-scale collection of phenomic, genomic, and transcriptomic data from hybrid crops. Artificial intelligence-driven genomic selection analysis is then applied to identify key genetic loci governing defense heterosis. Subsequently, functional validation of candidate loci elucidates their underlying molecular mechanisms. Based on this integrated genetic and molecular insight, precise gene editing is employed to engineer defense-heterosis-related loci in high-yield hybrid varieties, ultimately achieving the simultaneous enhancement of defense and yield. The image was created with BioRender.com, with permission.

thereby transcending the limitations of conventional phenotypic screening. Existing research indicates that the function of individual genes influences the formation of heterosis. For instance, as discussed in the main text, genes such as *FNS*,[40] *SFT*,[41] and *SHELL*[42] exert critical regulatory effects on specific traits through their heterozygous allelic states. Future research should prioritize the identification of key overdominant genes mediating defense heterosis. Utilizing precise gene-editing technologies such as CRISPR/Cas9 to modify corresponding loci in high-yield hybrid crops could offer innovative strategies to overcome the persistent challenge of simultaneously achieving both yield and defense heterosis.

Molecular studies have clarified that SA is a key signaling molecule inducing defense heterosis. Furthermore, the accumulation level and temporal dynamics of SA constitute central regulatory nodes that determine whether biomass heterosis can be concurrently achieved. Emerging evidence reveals that this dose- and time-dependent dual regulation of SA relies on rhythmic epigenetic mechanisms, including DNA methylation, histone modifications, and chromatin remodeling. A highly promising research direction is to employ CRISPR/dCas9-mediated epigenetic editing[91,92] or synthetic biology strategies to precisely engineer modules that fine-tune SA dynamics in crops. This approach could confer broad-spectrum and durable disease resistance while maintaining high and stable yields.

From an environmental perspective, crops face a complex microbial rhizosphere, which includes both beneficial symbiotic microorganisms and potential pathogens.[93] Recent research indicates that the biomass heterosis in maize is dependent on the composition of specific rhizosphere microbial communities. Altering the structure of the rhizosphere microbiota not only significantly influences the level of heterosis but also may even reverse it into hybrid disadvantage.[94] Therefore, screening combinations of rhizosphere microbiota that enhance defense heterosis offers an ecological solution at the agroecosystem level to the prevalent issue of weak disease resistance in crops. Furthermore, plants possess sophisticated microbial recognition mechanisms, such as the discrimination system between symbionts and pathogens mediated by LysM receptors.[95] When screening candidate genes related to disease defense heterosis in the future, greater attention should be paid to key components in the plant pattern-triggered immunity pathway to gain deeper insights into the regulatory mechanisms of microbe–plant interactions in the formation of defense heterosis.

In conclusion, by integrating multidisciplinary approaches to deeply dissect the causes and regulatory networks of defense heterosis,[96–98] and by developing novel strategies for its precise prediction and targeted engineering,[99,100] we will pave the way for overcoming the bottleneck in synergistically improving crop high-yield potential and durable disease resistance. This

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integrated effort will open new, effective pathways to safeguard global food security (Figure 4).

AUTHOR CONTRIBUTIONS

Kaiqi Xu: Conceptualization; methodology; writing—original draft; writing—review and editing; formal analysis. **Xue Li**: Writing—review and editing; writing—original draft. **Fangfang Li**: Conceptualization; methodology; writing—original draft; writing—review and editing; project administration; supervision; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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