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Review

Studies on the Molecular Basis of Heterosis in *Arabidopsis thaliana* and Vegetable Crops

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Abstract: Heterosis is an important phenomenon for high-yield crop breeding and is utilized for breeding F_1 varieties in horticultural crops. However, its molecular mechanism has not been elucidated, and compared to cereals, heterosis is less explored at the molecular level in horticultural crops. In this review, we compiled the new genetic and epigenetic studies on heterosis in horticultural crops. Because of the difficulty of predicting the level of heterosis from the parental genetic distance, molecular approaches are being used to study its molecular basis in horticultural crops. Transcriptome analyses in vegetables have identified photosynthesis-related genes as important in heterosis. Analysis of noncoding RNAs has suggested their involvement in regulating the heterosis of vegetative and fruit tissues. Quantitative trait locus (QTL) analysis has revealed the association of heterozygosity of a specific locus or multiple loci with heterosis of vegetative and fruit tissues. A higher level of DNA methylation was noted in the heterotic F_1 of *Brassica rapa* leafy vegetables, while the roles of other epigenetic modifications such as histone marks have not been explored.

Keywords: hybrid vigor; genetics; transcriptome; epigenetics; QTL; noncoding RNAs; DNA methylation; histone modification

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1. Introduction

It is known that the F_1 (first filial generation) resulting from a specific combination of parental lines can show traits superior to those of the parental lines; this phenomenon is known as hybrid vigor or heterosis. The discovery of this phenomenon dates back to the 19th century and is described in *The Effect of Cross- and Self-Fertilisation in the Vegetable Kingdom* in 1876 by Charles Darwin [1]. The word "heterosis" was introduced by George Shull instead of the ambiguous phrases, "stimulus of heterozygosis" or "heterozygotic stimulation" [2]. In plants, heterosis is accompanied by increased size and is also found in many crop and vegetable yield traits [3,4]. Heterosis occurs in livestock (animals) with greater milk, egg, or wool production [5]. The use of commercial F_1 varieties began with the incorporation by George Shull of increased yield through heterosis into a breeding program in maize. In Iowa, in the U.S., where the introduction of hybrid corn was earlier than in other states, the share of hybrid corn of the total maize planting increased rapidly from 1935, reaching 90% in 1939 [3]. After replacing the double cross methodology, where both parents were hybrids, with the single cross methodology in the 1960s, by 2000 the yield was further increased by 140 bushels per acre and was about five times higher than before the use of hybrids (open-pollinated inbred lines) [3].

The genetic mechanism of heterosis has long been discussed. There are some hypotheses ("dominance hypothesis", "overdominance hypothesis", "pseudo-overdominance hypothesis", and "epistasis hypothesis") that have been proposed to explain heterosis.

Under the dominance hypothesis, heterosis occurs when dominant alleles of one parent complement deleterious recessive alleles of the other parent in the F_1 [3,6,7]. Based on this dominance hypothesis, an inbred line, which shows the same level of growth as the heterotic F_1, can be created by accumulating dominant alleles. The accumulation of six dominant quantitative trait loci (QTLs) in sorghum could produce biomass that was equivalent to the heterotic F_1, indicating that biomass heterosis in sorghum could be explained by the dominance hypothesis [8]. Hybrid mimics (inbred high-yielding lines), selected for superior growth and showing growth comparable to the heterotic F_1 in *Arabidopsis thaliana*, wheat, and rice, may also be due to the accumulation of dominant alleles [9–12]. Under the overdominance hypothesis, heterozygosity itself results in heterosis and was formulated to explain the fact that few inbred lines approached the yield of the heterotic F_1 [3,13]. In tomato, a heterozygote between a functional and nonfunctional *SINGLE FLOWER TRUSS* gene (*SFT*/*sft*) increased the yield by up to 60% compared with plants having either a homozygous functional or nonfunctional gene [14]. In some cases, overdominance is actually pseudo-overdominance, which is caused by dominance complementation of two recessive mutations at closely linked loci in *trans* or in repulsion [15]. The dominance hypothesis, overdominance hypothesis, and pseudo-overdominance are based on allelic interactions of gene activity. The epistasis hypothesis is based on nonallelic interactions derived from the parental lines leading to heterosis [16]. The genetic mechanism of heterosis is complicated, especially for yield heterosis, as many loci are involved in heterosis, and cumulative effects of dominance, overdominance, pseudo-overdominance, and epistasis could be important for heterosis [17,18]. Despite a century of examination, these hypotheses cannot fully explain the mechanism of heterosis, but they are still a cornerstone of heterosis research.

The most labor-intensive part of the F_1 hybrid breeding process is finding the best parental combinations. The diallel cross where all parental combinations are crossed to make the F_1 plants is particularly labor intensive. Estimation of optimal parental combinations by molecular markers is desired. Initially, it was considered that the genetic distance between parents would have the potential to predict the combination of parental lines displaying the largest heterotic effects. Some studies showed that more genetically divergent parents could lead to increased heterosis, but a positive correlation between genetic distance and heterosis was not always present [19]. In a tomato study, crosses showing significant best parent heterosis (BPH) in some traits were derived from parents having a close genetic distance, although another F_1 derived from parental lines with a close genetic distance showed no significant BPH, indicating that genetic distance is not a predictor for heterosis in tomato [20]. There was also difficulty in predicting heterosis using the genetic distance of parental lines found in eggplant [21]. In the case of Chinese cabbage, there was a significant correlation between the genetic distance of parental lines and mid-parent heterosis (MPH) or between the genetic distance of parental lines and high parent heterosis (HPH)/BPH in some traits [22]. However, no such correlation was observed for plant weight at the harvesting stage (yield), consistent with the result of another study (Figure 1) [23]. The prediction of heterosis by genetic distance of parental lines is still under debate. It is difficult to predict heterosis from genome-wide genetic distances, and a limited number of chromosomal regions could be involved in heterosis.

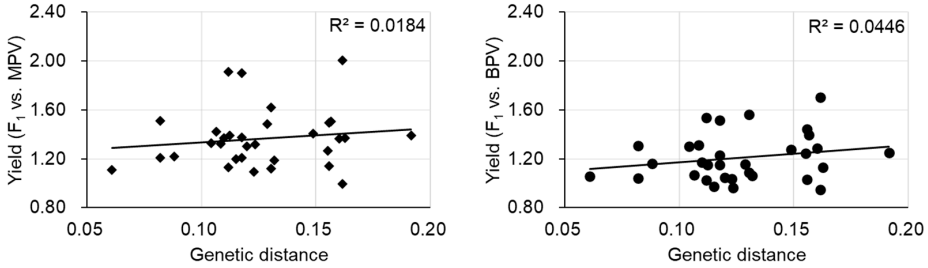

Figure 1. The relationship between yield heterosis and genetic distance of parental lines. MPV, mid-parent value, BPV, best parent value. Data are from [23].

Plant breeders have widely exploited heterosis for developing F_1 varieties in cereals and vegetables [19,24,25]. F_1 varieties not only show superiority in yield but also have stress tolerance and uniformity of growth in the field and size of products [19,26]. New F_1 vegetable varieties are replacing open-pollinated varieties; the top five vegetables with the highest number of F_1 varieties registered in Europe are tomato, pepper, melon, cucumber, and onion, in that order [27]. An effective, efficient, reliable, and stable method for F_1 seed production without contamination by self-fertilized seeds from each parent is useful for F_1 hybrid breeding [19,28]. For the commercial production of F_1 seeds, there are many genetic systems such as cytoplasmic male sterility, genetic male sterility, and self-incompatibility [28–31]. Hand-pollination systems are also used for producing F_1 seeds in some vegetables.

There has been a recent increase in heterosis research in vegetables. This review surveys the progress of the molecular basis of heterosis research in vegetables.

2. Heterosis Research Findings in *A. thaliana*

2.1. Genetic Analysis

To understand the genetic basis of the heterosis mechanism, QTL analysis and genome-wide association studies (GWAS) have been performed in *A. thaliana* [19,32,33]. QTLs of biomass or rosette diameter at 22 and 29 days after sowing (DAS) were identified on all chromosomes using a population derived from crossing between C24 and Columbia-0 (Col-0) accessions, and the overdominance model was mainly supported [34]. QTL analysis of biomass and leaf area at early developmental stage using recombinant inbred lines-test cross (RIL-TC) and introgression lines-test cross (IL-TC) from crossing between C24 and Col-0 identified QTLs on chromosomes 1, 3, and 4 [35]. Metabolite QTLs using RIL and IL populations derived from crossing between C24 and Col-0 were also identified, and hot spots of QTLs were observed on chromosomes 1, 3, and 4 [36]. Integration of QTL mapping using C24 and Col-0 accessions and systems biological network analysis revealed that overlapped genes of these two approaches are involved in biomass-related pathways [37]. Furthermore, multiple genes located in each QTL region, especially in chromosomes 2 and 4, might be involved in biomass heterosis in early development [37].

The genetics of the hybrid phenotype were explored by a GWAS in 30 inbred accessions and 435 hybrid combinations. A number of significant SNPs related to the MPH of dry mass were detected [32]. GWAS for biomass heterosis using 200 hybrids by crossing Col-0 with other accessions were performed, and no clear signals resembling a peak were observed, suggesting that many alleles could be involved in biomass heterosis [33]. Heterosis positively associated with 750 SNPs was identified using a modest significance threshold. Genes containing these SNPs were enriched in response to stimulus pathways, suggesting that genomic divergence of stimulus-responsive genes between parental lines might contribute to biomass heterosis [33]. These two studies did not identify a strong correlation between the genetic distance of parental lines and biomass heterosis, suggesting that a small number of genomic loci contribute to biomass heterosis [32,33].

2.2. Transcriptome

Transcriptome analysis such as microarray and RNA-sequencing (RNA-seq) has been used in heterosis studies of *A. thaliana*. Many attempts to pinpoint key genes associated with heterosis have been conducted by identifying differentially expressed genes (DEGs) between parental lines and their F_1s, and the average expression levels of parental lines, the mid-parent value (MPV), and F_1s have been compared [19,38]. When expression levels are different between the two parental lines, the same expression level between MPV and F_1 is called additive expression, while a different expression level is considered non-additive expression [19]. A difference in expression between the two parental lines with the expression level of the F_1 being the same as the parent with the higher expression level is considered high-parent dominance. The expression level of the F_1 being the same as the parent with the lower expression level is described as low-parent dominance. Using

SNPs in transcripts, it is possible to identify genes showing allele-specific expression in the F_1 [19,39]. In general, most genes in the F_1 showed additive expression, and the number of non-additively expressed genes is far fewer than additively expressed genes (Figure 2) [19,38,39]. Furthermore, the expression pattern in the parental lines and the F_1 is tissue- and stage-specific, making it difficult to examine the association between DEGs and heterosis from the profile of only a specific tissue or stage [19].

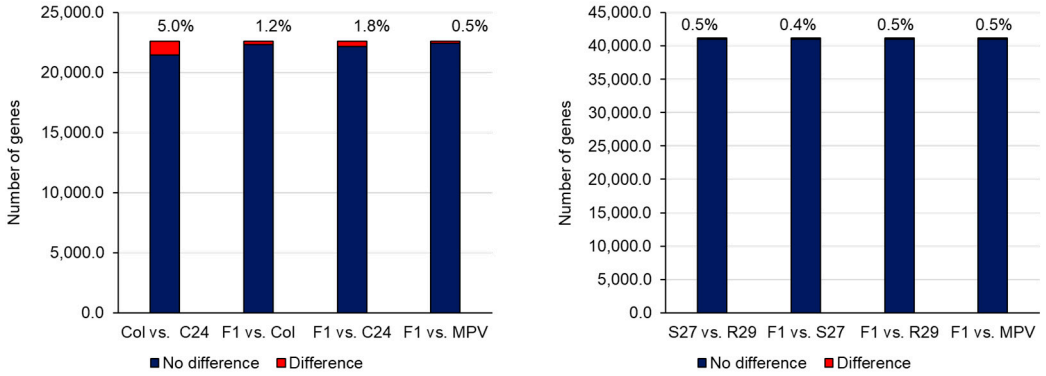

Figure 2. The number of differentially expressed genes in ten days seedlings of *A. thaliana* and two days cotyledon of *B. rapa*. The data were from [38,39].

Because the heterosis phenotype is superior to that of the parental lines, there has been a tendency to focus on non-additively expressed genes and associated overdominance or underdominance. Non-additively expressed genes categorized into 'chloroplast', 'photosynthesis', 'circadian rhythm, 'stress response', 'senescence', or 'plant hormone pathway' have been identified, and the association between non-additively expressed genes and heterosis discussed [38,40–46]. On the other hand, a similar expression pattern between one parent and the F_1 with developmental stage specificity might be important for heterosis [47]. Furthermore, the idea that the functional category showing high or low parent expression pattern changes through development could be important for heterosis has been proposed; a high parent expression pattern with the parent Per-1 in genes categorized into the photosynthesis pathway at 3–5 DAS (cotyledon developmental stage) and high parent expression pattern with another parent Col-0 in genes categorized into cell cycle pathway at 6–8 DAS (first true leaf developmental stage) were observed in the F_1, suggesting that coordinated gene expression and functional complementation during plant development is important for heterosis [48].

N6-methyladenosine (m^6A) is the most common covalent modification in mRNA and long noncoding RNA (lncRNA) [49,50]. Recently, many studies suggested that the modification of m^6A regulates plant development [51]. Xu et al. [52] mapped m^6A methylation of Col-0, Landsberg *erecta* (L*er*), and their F_1s, and the peaks of m^6A were conserved among them; most m^6A peaks (~95%) had an additive pattern in the F_1 and only a few hundred peaks showed a non-additive pattern. About 7% of non-additively expressed genes showed a non-additive pattern of m^6A modification. mRNA m^6A modification has been proposed as a new component of heterosis [52], but further research is needed.

2.3. Epigenetics

Epigenetics can give rise to heritable changes in gene regulation without alterations of the DNA sequence [53]. One epigenetic system is DNA methylation, which is the methylation of cytosine residues, and it occurs in all cytosine contexts, namely CG, CHG, and CHH (H = A, T or C) [53,54]. Another epigenetic system is histone modification, such as methylation, acetylation, ubiquitylation, phosphorylation, and sumoylation of histone tails [53,54]. Genome-wide analysis comparing DNA methylation states or histone modification states between parental lines and their F_1s showed additive states in the majority of genomic regions in F_1s [41,55,56]. DNA methylation rarely appears or disappears in the

regions without or with DNA methylation in both parental lines, respectively [41,55]. In regions where DNA methylation differs between parental lines, trans-chromosomal methylation (TCM) and trans-chromosomal demethylation (TCdM), which result in non-additive DNA methylation states in the F_1, occur [55,57]. RNA-directed DNA methylation (RdDM), which is mediated by 24-nucleotide small interfering RNAs (24-nt siRNAs), is involved in these TCM and TCdM events [57,58]. An F_1, which has a mutation of genes involved in the biosynthesis of 24 nt siRNAs, showed a similar level of heterosis to the wild-type F_1, suggesting that 24 nt siRNAs do not play a significant role in heterosis [57,59]. The weak association between non-additive DNA methylation states and non-additive gene expression makes it difficult to explain the contribution of DNA methylation to heterosis. However, F_1s between lines with the same genetic background and different levels of DNA methylation states showed growth vigor in certain combinations, suggesting that DNA methylation may be important for heterosis [60,61]. Furthermore, the level of heterosis decreased when the *decrease in DNA methylation 1* (*ddm1*) homozygous mutations were present [59,62]. As DDM1 is involved in the maintenance of DNA methylation, these results suggest a contribution of DNA methylation to heterosis. However, it is not clear why the loss of DDM1 function reduces heterosis, and further studies are needed [63].

2.4. Trade-Off between Growth and Disease Resistance

There are reports of the effect of heterosis on stress tolerance, including a role in freezing tolerance or disease resistance in *A. thaliana* [19]. Since heterotic F_1s with both increased biomass and disease resistance are rarely seen, a model for a trade-off relationship between defense and growth has been proposed [64,65]. Hybrid necrosis showing growth abnormalities due to autoimmunity-like responses has also been considered as a basis for this trade-off hypothesis [66]. Enhanced salicylic acid (SA) biosynthesis that regulates plant development and plant defense response contributes to the heterosis of disease resistance [65]. An elevation of salicylic acid accumulation promoted by a central circadian oscillator, CIRCADIAN CLOCK ASSOCIATED1 (CCA1), enables disease resistance heterosis. This F_1 also showed enhanced growth heterosis, and CCA1 is also involved in the growth heterosis, suggesting that CCA1 contributes to the balance between defense and growth heterosis [67]. The possibility that SA is involved in growth heterosis has been reported; decreasing SA level in the F_1 compared with MPV might cause growth heterosis [42]. However, the SA contents in heterotic F_1s are lower than those in the C24 parent and higher than those in the Col/L*er*/Ws parent [42]. F_1s with increased SA show both growth heterosis and no growth heterosis [65,67]. Alternately, there may be an optimal concentration of SA for growth heterosis; heterosis is associated with increased SA at low concentrations, but inhibition is associated with high concentrations [62]. Direct evidence of the relationship between SA content and growth heterosis is needed.

3. Heterosis in Leafy Vegetables

3.1. The Heterosis Phenotype in Vegetative Tissues

A superior phenotype of around 25% taller cross-pollinated progeny than the inbred lines of maize was first observed by Charles Darwin [1] and rediscovered by George Shull [68] and Edward East and Donald Jones [69]. After the discovery of heterosis, there was no doubt about the appearance of heterosis in morphological traits at the adult stage, but now, researchers have evidence of heterosis at the early developmental stage [19,70]. In *A. thaliana* F_1s, the heterosis phenotype has been found in different vegetative-tissue-related traits such as cotyledon size, leaf size, number of branches, rosette branching, rosette diameter, and fresh weight at the different developmental stages post-germination [19,33,38,42,46,71–76]. Depending on the crop and developmental stage from post-germination to final yield, various levels of heterosis have been observed in a variety of vegetative-tissue-associated morphological traits in F_1 hybrid vegetables such as Chinese cabbage [19,23,39,77], cabbage (*Brassica oleracea*) [78], cauliflower [79], rapeseed or canola (*Brassica napus*) [80–85], tomato [86–88], and eggplant [89–92]. Similar to vegetables, F_1s

showed heterosis in different vegetative tissues at early and harvesting stages in cereals such as maize [93–98], rice [99–102], and wheat [103].

In *A. thaliana*, leaf area heterosis did not occur by an increase in the photosynthesis rate per unit area but the total photosynthesis was increased due to the larger leaf area [38]. Cell division and/or cell elongation cause a larger cotyledon or true leaf area in F_1s [19,38,39,74], and the larger cotyledon or true leaf area increases the chloroplast number that ultimately increases the total amount of photosynthesis and photosynthate. Larger cotyledons in F_1s with more total photosynthesis might lead to a larger leaf size at the true leaf stage [19,39,46]. Higher photosynthesis capacity in an F_1 compared to the parents was also observed in maize [94–98] and rice [99]. Shoot dry weight heterosis of *A. thaliana* F_1s (Col-0/C24) was studied under different light intensities, where doubling of light intensity from 120 to 240 μmol m^{-2} s^{-1} produced about 2.5 times higher MPH in 15- and 28-day-old plants [72], and the same correlation between photosynthesis and light intensity was found in *A. thaliana* [38]. These results suggested that photosynthesis and its associated factors play a role in the heterosis phenotype in the vegetative tissues of F_1s, especially at the early developmental stage.

3.2. A Case Study in Brassica Vegetables

In *Brassica* leafy vegetables, heterosis of vegetative biomass is commercially important. Heterosis can be seen from the early developmental stages in Chinese cabbage (Figure 3) [39,77]. Biomass yield heterosis in cabbage (*B. oleracea*), pak choi, and non-heading and heading Chinese cabbage was also shown (Figures 4 and 5) [22,23,39,77,104–107]. In the case of Chinese cabbage, biomass heterosis in vegetative tissues is due to increased leaf area and weight rather than increased leaf number [39,77]. In broccoli (*B. oleracea* var. *italica*), heterosis is observed not only in leaf size but also in curd size, which is a determinant of the economic value [108].

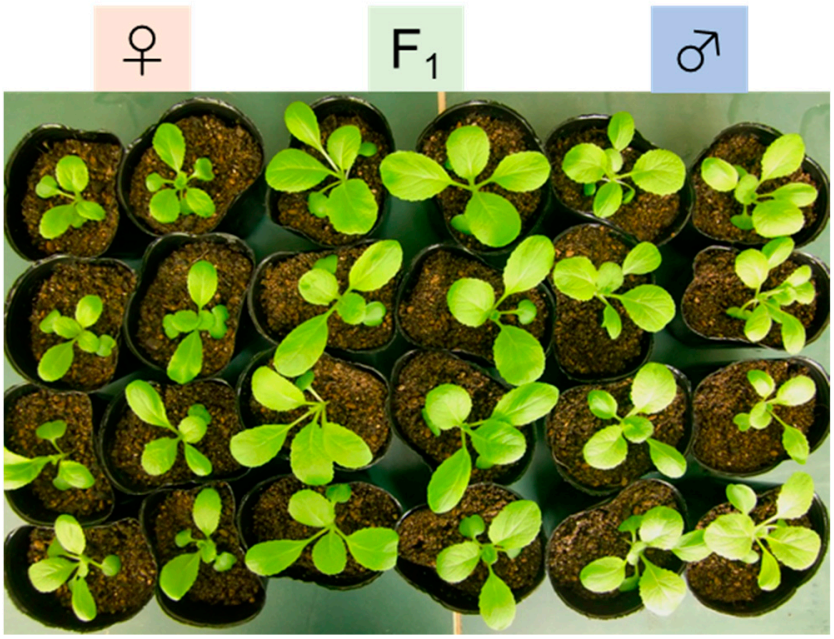

Figure 3. Increased plant size in F_1 (W39) compared with parental lines (S27 female inbred and R29 male inbred line) at 18 days after sowing in Chinese cabbage. The data are from [39].

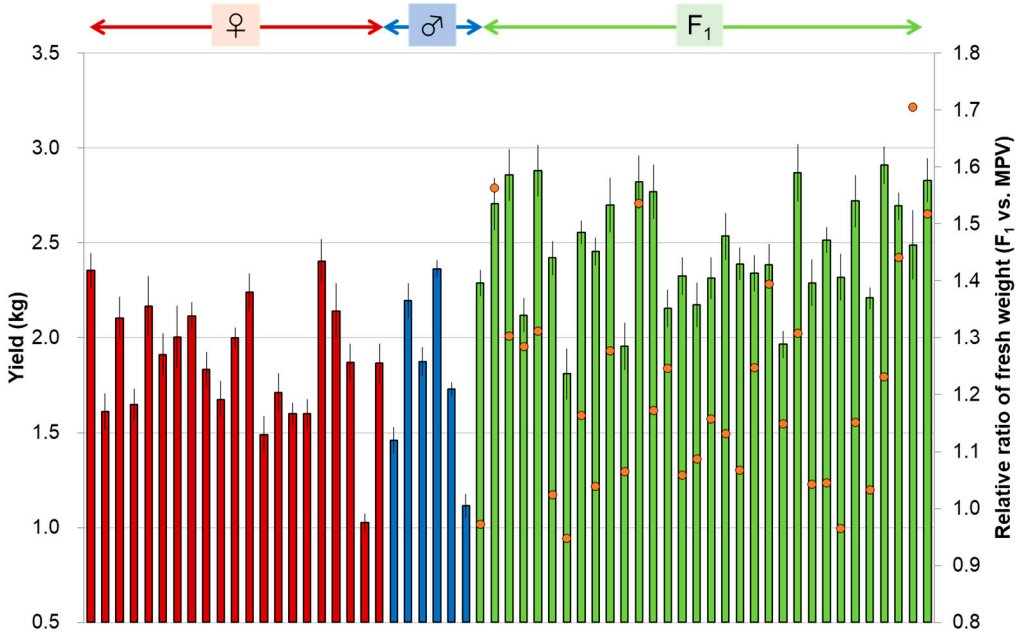

Figure 4. The level of yield heterosis in Chinese cabbage. The data are from [23]. Orange circles represent the ratio of fresh weight compared between the F_1 and the mid-parent value (MPV).

Figure 5. Heterosis of head size in an F_1 hybrid of Chinese cabbage.

Transcriptome analyses were performed on broccoli, cabbage, pak choi, and non-heading and heading Chinese cabbage [39,77,104–106,108,109]. In four cabbage F_1s and their parental lines, the outer layer of head leaves when 80% of the head leaves were at commercial maturity were used. F_1s showed dominant expression patterns, and the proportion of maternal expression level dominance was higher than that of paternal expression dominance, suggesting that expression dominance with a maternal bias is important for heterosis in cabbage [106]. In 70-day-old curds of broccoli, fewer than 1% of total genes showed a non-additive gene expression pattern, suggesting that genes with additive expression in the F_1s might be important for heterosis in broccoli [108]. Genes involved in response to abiotic and biotic stress tended to show differential expression between F_1s and their parental lines in curds of broccoli [108]. In heading Chinese cabbage, transcriptome analyses on cotyledons at 2 DAS, leaves at 40–50 DAS, or the first leaf at 15 DAS and 60 DAS showed that genes involved in photosynthesis, cell division, cell proliferation, response to plant hormone, and response to abiotic stress tended to show differential expression between F_1s and their parental lines at different developmental stages [39,77,109]. Similar to *A. thaliana* and canola, genes involved in photosynthesis and chlorophyll biosynthesis were upregulated in the F_1 compared to MPV at the 2-day-old cotyledon stage in Chinese cabbage [38,39,82]. In the first leaf at 15 DAS and 60 DAS, differentially expressed genes in F_1s and their parental lines tended to show high parental expression level dominance [77]. In pak choi, genes involved in 'photosynthesis', 'thylakoid', and 'chloroplast' categories

tended to show differential expression between parental lines and F_1s in leaves of one-month-old plants. Upregulation of *BrLhcb1* in F_1s was identified, and this may result in higher expression levels of *BrCCA1* in hybrids at Zeitgeber time 4 (ZT4) and increased photosynthesis. Silencing and overexpressing *BrLhcb1* were associated with decreased and increased number of grana thylakoids, respectively, suggesting that higher expression of *BrLhcb1* in F_1s might be associated with enhanced photosynthetic capacity [105]. It is possible that this could be a contributing factor to heterosis in pak choi. Overall, photosynthesis-related genes tended to have higher expression levels in F_1s, but this is not always associated with increased photosynthetic capacity. There have been reports of an association between light and heterosis [12,72], circadian rhythm and heterosis [40,67], and chlorophyll biosynthesis and heterosis [38,39], suggesting that photosynthesis-related genes may be associated with increased plant size, such as increased cell size or cell number.

Micro-RNA (miRNA) expression patterns in F_1s and their parental lines were examined in the first leaf of Chinese cabbage at 15 DAS and 60 DAS [77]. The 63 and 51 miRNAs showed differences in the expression level between F_1s and MPV at 15 DAS and 60 DAS, respectively, and most had low parental expression level dominance [77]. Genes involved in leaf morphogenesis and leaf shaping were over-represented in the target genes of miRNAs with low parental expression level dominance. For example, bra-miR319, bra-miR156, and bra–miR5722 that target *BrLHCB1.2* showed low parental expression level dominance and *BrLHCB1.2* showed upregulation in F_1s. Similarly, bra-miR391 and bra-miR396 that target *BrGRF4.2* also showed low parental expression level dominance, and *BrGRF4.2* was upregulated in F_1s. Overexpression of *BrGRF4.2* and bra-miR396 in *A. thaliana* showed increased and decreased vegetative biomass, respectively. This study suggests that the low parental expression level dominance of miRNAs is involved in the heterosis mechanism in Chinese cabbage [77].

Genome-wide DNA methylation states in F_1s and their parental lines were examined by whole-genome bisulfite sequencing using leaves of one-month-old plants of pak choi. Higher levels of DNA methylation at CG, CHG, and CHH sites, especially in the promoter regions, were found in F_1s compared with the parental lines [105]. In broccoli, genome-wide DNA methylation levels of CG and CHG sites in F_1s and their parental lines were examined by MethylRAD methods. DNA methylation levels in F_1s were slightly higher (0.90–1.36%) than in parental lines, but DNA methylation levels in F_1s were additive. Differentially methylated regions among F_1s and their parental lines were mostly in intergenic regions [108]. Some genes showed differential methylation levels between F_1s and their parental lines, but this did not lead to a change in gene expression levels [108]. Increased DNA methylation levels were also found in heterotic F_1s in canola and *A. thaliana* [41,110], but most sites are additive. In addition, although some genes showed differences in DNA methylation levels, there are few cases where this has an effect on gene expression levels. The impact of these changes in DNA methylation levels in F_1s on heterosis is still largely unknown.

Yield-related traits where heterosis is observed are quantitative traits controlled by a number of genes [111,112]. QTLs related to yield-related traits were identified in Chinese cabbage and cabbage. Two dominant genetic regions, one at chromosome C02 and one at C03, for yield-related traits including economic yield and head size were identified in cabbage (*B. oleracea*). Both of these QTLs are due to the genetic effect of the elite parent line (01–20) [107]. Four QTLs for plant weight (in chromosomes A01, A05, A07, and A08) were identified using the F_2 population derived from a heterotic F_1 of Chinese cabbage (Figure 6) [113]. The QTL in A08 has a pleiotropic effect on head leaves, height, diameter, and weight, where a 23.6% phenotypic variation was found in total numbers of head leaves, suggesting a dominant effect of the QTL in A08 for the heterosis in plant weight [113]. QTL analysis using doubled haploid populations or a population of RILs derived from F_1 crossing of two Chinese cabbage inbred lines was performed, and three QTLs in chromosomes A01, A03, and A07 were commonly detected in two populations (Figure 6) [114]. QTL analysis using a doubled haploid population or an F_2 population

from F_1 crossing heading Chinese cabbage and non-heading pak choi was performed, and two QTLs for head weight were detected on chromosomes A06 and A08 using the F_2 population, although estimated genetic variation in each QTL is small (Figure 6) [115]. Yield is sensitive to environmental influences and the effect of each QTL is not large, making it difficult to identify the causative gene, but heterosis may be explained by the accumulation of heterozygosity in multiple regions. This would link to the fact that genetic distance between parental lines at whole-genome levels cannot predict yield heterosis with high accuracy.

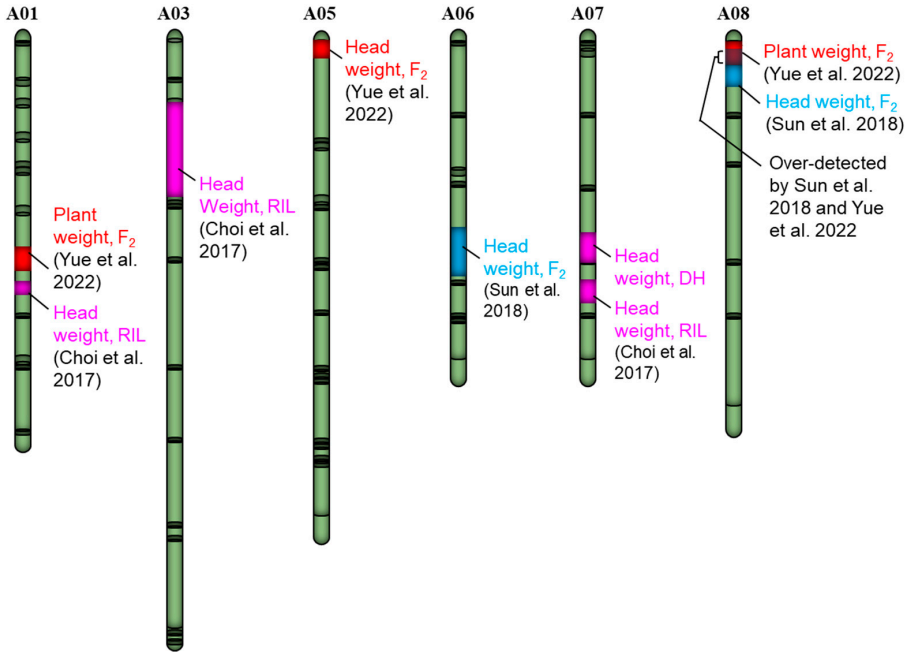

Figure 6. Chromosomal locations of yield heterosis in Chinese cabbage found by Yue et al. [113], Choi et al. [114], and Sun et al. [115].

4. Heterosis in Fruit and Root Vegetables

In fruit vegetables, the number of fruits or fruit size is directly associated with yield, so the findings in cereals will be helpful in understanding fruit vegetable heterosis. In rice, yield heterosis is associated with grain number per panicle and thousand-seed weight, and the timing of heading is also an important factor for yield heterosis [18]. In canola, the F_1 showed heterosis in silique number and grain yield [110]. In tomato in 10 parental lines and 45 hybrids, the average score of yield and fruit number per plant in the F_1 was significantly higher than in parental lines [116]. In eggplant, heterosis in fruit sizes (fruit length, girth, and weight) and fruit number (number of branches and the number of fruits per plant) was observed [92]. In capsicum, the heterotic F_1 has a higher yield, fruit weight, and fruit diameter than parental lines [117], and the number of fruits per plant showed heterosis and a high positive correlation with yield [118]. Heterosis in the accumulation of metabolites was observed in tomato [20], and heterosis of capsaicinoid accumulation in chili pepper was observed [119].

The relationship between the genetic distance between parents and yield heterosis has been examined in fruit vegetables such as tomato [20], eggplant [21,120], cucumber [121], capsicum [122], and melon [123,124], and there is a negative or no correlation between them, suggesting that the genetic distance between parents is not a strong predictor for yield heterosis in fruit vegetables.

Studies on combining abilities of agronomic traits using diallel mating help to predict gene action (additive or non-additive) of heterosis using the ratio of general combining ability (GCA), which is superior in any cross, and specific combining ability (SCA), which is superior only in certain combinations [125]. A full diallel mating using five parental

accessions in tomato showed BPH not only in agronomic fruit traits but also in metabolites. In agronomic fruit traits, GCA tended to be higher than SCA, suggesting that an additive mode of gene action is associated with agronomic fruit traits. In metabolites, the GCA/SCA ratio tended to be lower than 1.0, suggesting that the non-additive mode of gene action contributes to the metabolite level [20]. A difference in hybrid performance was identified between reciprocal hybrids [20]. Diallel genetic analysis in eggplant showed a high range of GCA/SCA ratio among 28 traits, from 0.15 to 4.08, indicating the presence of both additive and non-additive effects. Yield showed the lowest GCA/SCA ratio in eggplant, representing non-additive effects [21]. In the full diallel mating analysis of melon, yield, fruit number, and fruit weight showed additive effects [126]. The contribution of additive, non-additive, or both modes of gene action to heterosis of yield-related traits in fruit vegetables depends on traits, breeding lines for diallel mating, and types of fruits vegetables [20,21,91,126–131].

Yield-related traits of fruit vegetables where heterosis is observed are also quantitative traits. Using the ILs of genomic fragments of the wild species *Solanum pennellii* introgressed into the elite inbred line M82, the over-representation of over-dominant QTLs in reproductive traits was observed, while this was not observed in non-reproductive traits [132]. Using the same IL population, a pyramiding of three yield QTLs showed a dramatic increase in yield, Brix, and Brix x yield, and the best genotype combination is homozygous for the *S. pennellii* allele at QTL on chromosome 7, heterozygous at QTL on chromosome 8, and homozygous for the *S. pennellii* allele at QTL on chromosome 9 [133,134]. For fruit vegetables, flowering time affects the yield, and the increased yield of tomato due to the increased number of fruits is regulated by the balance between the antagonistic effects of the floral activator, *SFT*, and the repressor, *SELF PRUNING* (*SP*) [16,135,136]. Loss of function of SFT results in delaying flowering leading to a decreased number of flowers/fruits, and loss of function of SP results in promoting sympodial shoot transition to flowering, thereby increasing the number of flowers/fruits. Plants having an *sft/SFT* heterozygous with *sp/sp* homozygous background showed increased fruit production and overdominance of yield heterosis involving a single gene [14]. This is due to the dosage effect of *SFT* optimizing shoot and inflorescence production, delaying the primary flowering transition weakly and seedling development and primary shoot meristem maturation [137]. Optimization of plant architecture related to increased sympodial shoots and inflorescences by the dosage sensitivity of allelic genes in the florigen pathway can improve the yield [138–140]. In melon, fruit size is important, and QTL analysis for fruit size using F_2 populations derived from crosses between wild and cultivated lines identified multiple QTLs [141–143]. The dominance effect of QTLs for the fruit shape (ratio of fruit length and diameter) was observed [144], while additive gene action was frequently observed in QTLs of fruit size [141]. Grafting is commonly used in melon, and rootstock-mediated yield heterosis by grafting on hybrid rootstocks using a common scion was examined. Out of 190 hybrids, 79 showed significant BPH, and heterozygosity in two QTLs was associated with increased rootstock-mediated yield, suggesting that the root function contributes to the yield heterosis in melon [124].

A transcriptome analysis between parental and F_1 lines of pepper at seedling and flowering stages showed that non-additive gene expression including overdominance, underdominance, high-parental dominance, and low-parental dominance was predominant [145]. The gene ontology analysis of DEGs between F_1 and its parental lines revealed the over-representation of 'primary metabolic process', 'photosystem', 'phosphotransferase activity', and 'kinase activity' [145]. A Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis showed that photosynthesis and plant hormone signal transduction pathways were found at both seedling and flowering stages either in high-parent dominant or over-dominant states, respectively [145]. The weighted gene co-expression network analysis (WGCNA) identified the hub genes that were related to β-glucosidase and auxin responsiveness [145]. About 30% of transcription factors differentially expressed between an F_1 and its parents showed high-parent dominance or overdominance [145]. Differentially expressed noncoding RNAs such as miRNAs, long noncoding RNAs, and circular RNAs

between F_1 and its parental lines at both seedling and flowering stages were also identified, suggesting their relationship with heterosis [145].

Epigenetic variation can explain the variation in growth behavior and is sometimes associated with the enhancement of vigor in plant size, suggesting that epigenetic variation might be associated with heterosis [63,146]. Inhibition of MutS HOMOLOG1 (MSH1) function induces alteration of plant development, and suppression of *MSH1* by RNA interference (RNAi) in tomato showed changes in leaf morphology, variegation, dwarfing, male sterility, flower development, and flowering time [147]. Sometimes these altered phenotypes were inherited to the next generations even though the transgene had been segregated out, suggesting that some altered phenotypic variation could be due to epigenetic variation (Figure 7) [147]. These epi-lines showed enhancement of seedling size and increased total fruit yield by increased fruit numbers (Figure 7). Progeny from the wild-type scion grafted to the MSH1-RNAi line as rootstock showed an enhanced early growth rate, suggesting that enhanced growth vigor is nongenetic [147]. This study sends us two important messages: one is that phenotypic variation by *MSH1* suppression is due to nongenetic/epigenetic changes, and the other is that phenotypic variation includes enhancement of the growth phenotype, in other words, the possibility that heterosis is regulated by epigenetic effects.

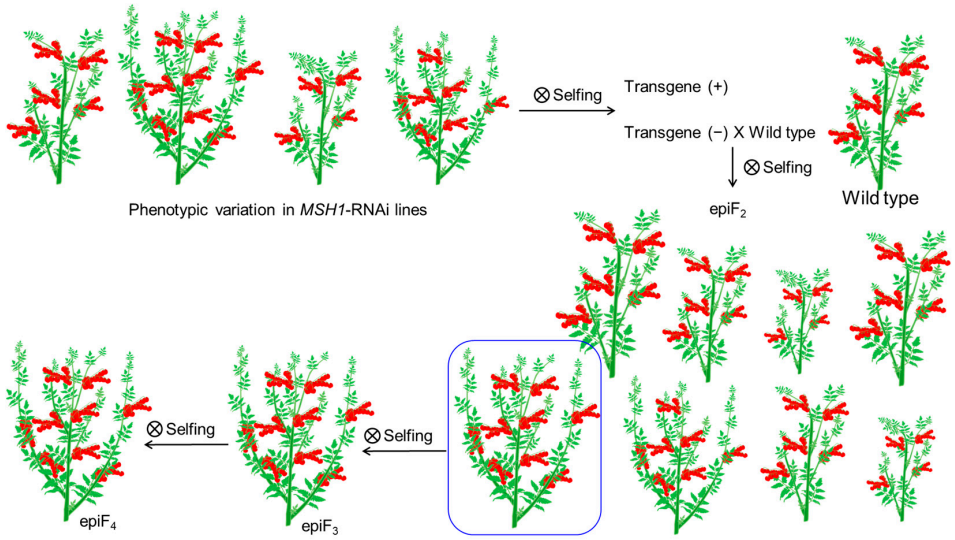

Figure 7. Epigenetic alteration of tomato phenotypes via *MutS HOMOLOG 1* (*MSH1*) suppression by RNA interference (RNAi). Transgene-null segregants derived from progeny of *MSH1*-RNAi transgenic plant were crossed to wild-type line; some F_2 plants, which are termed $epiF_2$, showed enhanced seedling growth and fruit yield relative to the wild type; and $epiF_3$ derived from single $epiF_2$, which showed enhanced seedling growth and fruit yield, also showed higher yield than in the wild type.

In root vegetables, although F_1 varieties have been developed in carrot and radish, research on heterosis of these vegetables is limited compared to leafy and fruit vegetables. Heterosis in root biomass in carrot was observed [148,149], and a moderate positive relationship between yield heterosis and genetic distance of parental lines was observed [148]. However, there are few reports of genetic, epigenetic, or multi-omics studies on carrot heterosis. Ogura cytoplasmic male sterility, which was originally identified in Japanese radish, is well known and used for F_1 seed production not only in radish but also in *B. oleracea* (cabbage or broccoli), *Brassica juncea*, and *B. napus* (canola) [28]. It is well known that yield heterosis (root) is observed in radish [150], but as with carrot, there have been few studies on heterosis by genetic, epigenetic, or multi-omics approaches. Cultivated potatoes are autotetraploid and are an important source of carbohydrates for humans. As potato is a clonally propagated crop, sales of seeds are not major; F_1 varieties have

not been developed. Thus, heterosis studies in potato are limited. However, strategies through seed sales of potato (hybrid potatoes) are being considered [151]. A heterosis study using homozygous diploid parental lines of potato was performed, and both reciprocal hybrids showed heterosis in vegetative size, flower size, and tuber yield [152]. Transcriptome analysis using seedling leaves, flowers, and developing tubers showed that 4–15% of genes were non-additively expressed. Metabolome analysis using the same tissues showed non-additive accumulation of metabolites that differed among three tissues. Primary metabolites showed positive mid-parent heterosis, while secondary metabolites showed negative mid-parent heterosis in seedling leaves and flowers. In tubers, negative mid-parent heterosis was observed in both primary and secondary metabolites. Methylome analysis showed additive DNA methylation levels [152].

5. Perspective

Vegetables are important for human health, and improvement in yield is essential to support future population growth; a stable supply is important from the viewpoint of food security. Heterosis has played and will play a role in satisfying this demand; F_1 varieties already have a large share of the market in some vegetables, and new F_1 varieties have been developed. In breeding, crossing of parental lines within the same subspecies (intra-subspecies hybrids) is generally used. In tomato, there is increased yield in plants containing introduced genomic fragments from wild species [132]. Thus, interspecific or inter-subspecies hybrids may show greater heterosis than intra-subspecies crosses. Increased vegetative biomass can be found in interspecific hybrids [153,154], but the differences in traits between the two species are so great that it is difficult to set evaluation criteria for heterosis. However, there may be potential in interspecific or inter-subspecies crosses in terms of improved yield potential.

Molecular breeding is effective, and in disease resistance, for example, breeding using marker-assisted selection (MAS) for resistance genes has been performed [155]. However, MAS has not been used to predict high-yielding parental combinations with high levels of heterosis. Information on combining abilities of agronomic traits using diallel mating and on QTLs related to yield has been accumulated. Since high-throughput genotyping is progressing, it can be expected that more loci related to yield will be identified and may support the use of MAS for F_1 breeding.

Integrated omics analysis such as transcriptome, metabolome, proteome, and epigenome have been conducted. RNA-seq is becoming more accessible and has been used in many horticultural crops. However, the RNA profile changes with tissue and stage. The proteome or metabolome could be closer to the plant phenotype than the transcriptome, so further characterization of these could be important and may identify biomarkers of heterosis. Although there is still insufficient information on the extent of tissue and stage variation in the epigenome in horticultural crops, there is some evidence that epigenetics is involved in heterosis [63], and further research is desirable to understand the molecular mechanism of heterosis.

Research has been conducted to understand the molecular mechanism of heterosis in various vegetables, and our understanding is advancing. With the accumulation of further research, the day will come when the proper parental combination for high levels of heterosis is predictable and heterosis is maximized using molecular markers.

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