Unintended Consequences of Plant Domestication

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Human selection on wild populations mostly favored a common set of plant traits during domestication. This process of direct selection also altered other independent traits that were not directly perceived or desired during crop domestication and improvement. A deeper knowledge of the inadvertent and undesirable phenotypic effects and their underlying genetic causes can help design strategies to mitigate their effects and improve genetic gain in crop plants. We review different factors explaining the negative consequences of plant domestication at the phenotypic and genomic levels. We further describe the genetic causes of undesirable effects that originate from the selection of favorable alleles during plant domestication. In addition, we propose strategies that could be useful in attenuating such effects for crop improvement. With novel -omics and genome-editing tools, it is relatively approachable to understand and manipulate the genetic and biochemical mechanisms responsible for the undesirable phenotypes in domesticated plants.

Introduction

Plant domestication underlies long-term selection on several desired characteristics of wild populations to meet the needs of early farming communities (Doebley et al. 2006). These phenotypes represent a common set of traits, also called as 'domestication syndrome' (Hammer 1984), which differentiates the domesticated plants from their wild ancestors. The most common domesticated traits across different species include loss of dormancy, larger organ size, reduced seed dispersal and shattering, uniformity in growth and change in day length sensitivity (Doebley et al. 2006, Olsen and Wendel 2013), mainly due to their high significance for successful adaptation, easy management and higher production under cultivated environments. A direct strong selection of 'domestication syndrome' traits led to the genetic analysis and subsequent cloning of genes controlling them (Doebley et al. 2006, Olsen and Wendel 2013). However, consequences of selection are not exclusive to directly targeted traits and genes during domestication. The wild and domesticated populations often remarkably differ for traits that escape direct selection during plant domestication (Heiser 1988, Zohary 2004, Purugganan 2019). Morphological and genetic analyses of some of these traits revealed that direct selection on desired traits led to an inadvertent selection of alleles controlling them (Fernández-Marín et al. 2014, Singh et al. 2019). Despite these findings, the type of traits under inadvertent selection and their underlying genetic control lack a thorough review. Moreover, domestication studies have led to the identification of genes and genomic regions for important plant traits (Doebley et al. 2006, Olsen and Wendel 2013), while studying traits under indirect selection can help cloning the gene regulators of potentially high value traits under current agronomic practices.

This review summarizes the research describing the inadvertent effects of selection during plant domestication. We further analyze the mechanisms and undesirable consequences of unintended selection of traits and genes during the plant domestication process. These insights will provide novel additions to the current understanding of the plant domestication process and its utilization for crop breeding and improvement.

Useful Traits Left Behind

Plant domestication preferentially targeted desirable traits that were either directly perceived by humans or critically important for cultivation under monoculture conditions. However, several important plant phenotypes were directly or indirectly left out during this process (**Fig. 1**). Some of these traits might have less or no importance at the start of domestication and were eventually left out during the long-term selection process. A few other traits escaped direct selection due to the lack of their perception by humans. With the advent of new genetics and -omics technologies, these hidden traits have been identified and characterized between wild and domesticated plant populations (Fernández-Marín et al. 2014, Singh et al. 2017, 2019, Luna-Ruiz et al. 2018, Wang et al. 2020, Pereira et al. 2021b). These studies highlighted that domestication-related selection has undesirable impacts on several beneficial traits, including but not limited to plant immunity, nutritional quality and flavor and adaptation.
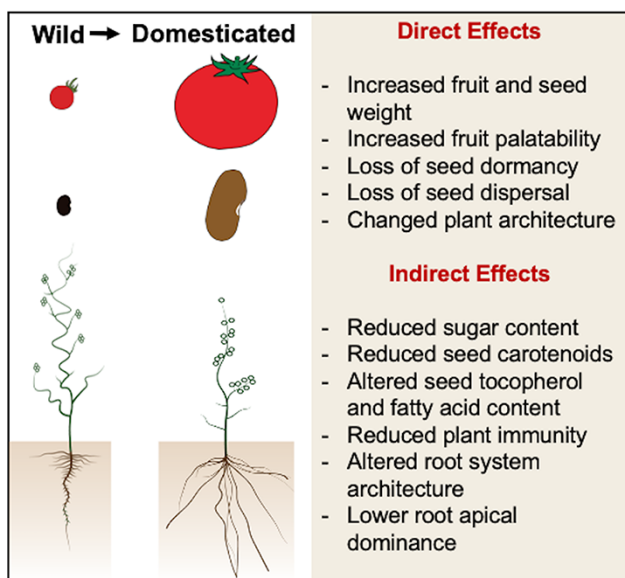
Fig. 1 An overview of direct and indirect changes resulting from plant domestication. Artificial selection of directly selected traits brought about indirect changes in other plant phenotypes.

Loss of innate plant immunity appears to be a common feature associated with domestication in many plant species (Hajjar and Hodgkin 2007)—the evolutionary and genetic significance of which is not very clear. The reduced frequency or complete loss of resistance alleles due to genetic drift can explain this phenomenon to some extent, especially when resistance is controlled by major gene/s in crop plants. Furthermore, the wild plants were under continuous pressure from diverse pathogens, and inherent genetic resistance was a necessary defense for their fitness and survival in natural habitats. In domesticated habitats, the extra care in agronomic measures and later, the application of chemicals slowly eliminated the need for natural pathogen immunity in cultivated plants. The loss of immunity during domestication should also be considered under the 'cost of resistance' hypothesis (Bergelson and Purrington 1996, Tian et al. 2003). For example, the presence of a single *RPM1* gene, conferring resistance against the bacterial pathogen *Pseudomonas syringae*, resulted in less shoot biomass, fewer siliques and less seed production in the resistant *Arabidopsis* ecotype during replicated field trails (Tian et al. 2003). Thus, keeping resistance genes may have associated fitness costs on desirable traits under selection during the plant domestication process. At the same time, selection of genetic pathways that have dual roles in quantitative resistance and other desirable traits could explain the loss of immunity in the domesticated plant forms. For instance, certain metabolic compounds such as steroidal glycoalkaloids (SGAs), guaiacol and methyl salicylates provide chemical defense and contribute to systemic plant immunity against diverse pathogens (Park et al. 2007, Dahlin et al. 2017, Chen et al. 2019). These metabolites are also associated with undesirable fruit flavor in tomato (Zanor et al. 2009, Tieman et al. 2017, Zhu et al. 2018), and increase in fruit palatability by selecting against these compounds might

have inadvertently compromised the host plant immunity. In fact, Zhu et al. (2018) have shown that a direct negative selection against fruit bitterness decreased the concentrations of 45 out of 46 SGA metabolites in domesticated compared to wild tomato accessions. The SGA compounds, although bitter and anti-nutritional, can act as a protective shield against diverse plant pathogens. A set of five major loci under selective sweeps contributed to the decrease in SGAs during tomato domestication. Although improving fruit flavor by reducing SGAs was a positive consequence of artificial selection, still it compromises the immunity of plants and making them more vulnerable to diverse pathogens. Hence, identifying the direct genetic causes of such relationships, as described by the role of SGAs in flavor and plant immunity, can help select high value loci with both good flavor and durable resistance against pathogens. These findings could also have implications in modern breeding programs, where selection for disease resistance remains a major goal for crop improvement efforts.

The metabolic diversity between wild and domesticated plants provides reasonable assumptions to address the undesirable effects of domestication. For example, while selection against seed dormancy, increased storability and dispersal, the seed carotenoid content inadvertently decreased in several widely consumed legumes including soybean, pea, common bean, peanut and chickpea (Fernández-Marín et al. 2014). In tomato, the trans-lycopene content for red fruit color is reduced from wild *Solanum pimpinellifolium* (SP) to semi-domesticated *Solanum lycopersicum* cerasiforme (SLC) accessions, which remained fixed afterward in the cultivated *S. lycopersicum* L. var. lycopersicum (SLL) (Razifard et al. 2020). Similarly, a meta-analysis revealed that wild species carry higher allelic diversity for fruit sugar contents compared to domesticated accessions (Zhao et al. 2019). Although the effects of domestication on tomato fruit flavor are not fully quantified at the level of volatiles, deterioration of flavor in modern tomato cultivars has been associated with significantly low quantities of flavor-specific chemicals (Tieman et al. 2017). Collectively, these results suggest that indirect selection of undesirable phenotypes occur through complex metabolic pathways in plants, which was implausible to capture at the start of domestication.

In a similar way, other unperceived plant traits shall most likely illustrate the undesirable impacts of artificial selection. Among them, root traits were neglected during the domestication of desirable above-ground plant parts, yet they differ significantly between wild and domesticated populations in different crops (Singh et al. 2019, Chen et al. 2021). A change in soil habitats and direct selection of above-ground plant parts may have caused these differences in roots of these two groups. Interestingly, wild plants are a source of key root traits that are important for adaptation under marginal conditions. For instance, wild common beans display a relatively high root apical dominance than the domesticated plants, which is an important trait under water stress conditions (Singh et al. 2019). In fact, wild accessions are able to penetrate the deep soil horizons under drought stress by allocating 60% greater root

to total plant biomass (Berny Mier Y Teran et al. 2019). Similarly, wild tomatoes appear to be less sensitive to salt stress than their domesticated counterparts (Wang et al. 2020). These traits could have been less important for domesticated plants to adapt to fertile and well-irrigated soils during the start of domestication, which led to their reduced phenotypic expression in them.

Genomic Consequences

Sifting out beneficial mutations

Loss of genome-wide genetic diversity in modern day crops is a typical signature of plant domestication. The extent and magnitude of the erosion of genetic variation differ depending on the strength of selection on trait/s under selection and individual domesticated plant genomes. For instance, the domesticated SLL and the semi-domesticated SLC tomatoes represented approximately 22.6% and 53.8% of the standing genetic diversity in the wild SP populations, respectively (Lin et al. 2014). Similarly, genetic diversity reduced to almost 50% from wild *Glycine soja* to soybean (*Glycine max*) landraces (Zhou et al. 2015) and 30–50% from wild to cultivated peppers (Qin et al. 2014). The genome-wide genetic diversity was similar in the domesticated and wild populations of apple (*Malus x domestica* vs. *Malus sieversii*) and potato (*Solanum tuberosum* L.) (Duan et al. 2017, Hardigan et al. 2017). In contrast, an increased genome-wide diversity was observed during common bean (*Phaseolus vulgaris* L.) domestication in the Andean region, whereas an opposite trend was found in the independent domestication of common bean in Mesoamerica (Schmutz et al. 2014). In the latter case, frequent gene flow between the wild and domesticated populations was proposed to be a likely cause for high diversity in modern common bean populations from the Andes (Schmutz et al. 2014).

Apart from the genome-wide effects on genetic diversity, strong selection mostly fixed the major mutations regulating a trait of interest, while minor variants associated with quantitative phenotypes might have been sifted out (Eyre-Walker and Keightley 2007). The latter could have happened due to selection and/or genetic drift. Some of these variants could represent the unique beneficial alleles contributing to the additive genetic variation for the same or different quantitative traits. There are several examples explaining this phenomenon in different plant species. For instance, fruit weight in tomato was a primary target of selection during domestication (Frary et al. 2000, Chakarbarti et al. 2013). Recently, a comprehensive evaluation of F_2 mapping populations, which originated from the semi-domesticated SLC tomato germplasm and fixed for the known fruit weight genes, showed segregation for fruit weight (Pereira et al. 2021). Subsequent genetic analysis using a quantitative trait locus (QTL)-Seq approach identified six novel QTLs for fruit weight in these populations—the favorable alleles of which were contributed by the SLC accessions from South America (Pereira et al. 2021). These beneficial alleles, although retained during a certain domestication timeframe, were eventually left

behind in modern and SLC accessions from other regions. Similarly, tomato pan-genome analysis revealed a severe loss of genes and promoters associated with disease resistance and fruit flavor during domestication (Gao et al. 2019). This analysis identified a rare allele of *LoxC*, whose expression in ripe fruits was associated with apocarotenoid and increased lipid-derived volatile production (Gao et al. 2019, Pereira et al. 2021a). The *LoxC* gene showed ancestral duplication in SP accessions (Pereira et al. 2021a), and it appears that the rare allele of *LoxC* was unintentionally left behind during tomato domestication (Gao et al. 2019).

The loss of useful mutations appears to be a recurrent theme in several domesticated crops. As discussed earlier, the most common examples include the lack of disease-resistance and adaptive alleles in the domesticated germplasm. For example, the domesticated common bean accessions showed lower innate immunity than the wild accessions against bacterial pathogens, *P. syringae* pv. syringae and *Enterobacter* sp. strain FCB1 (Córdova-Campos et al. 2012). A similar analysis using diverse wild and domesticated tomato accessions indicated that the response to disease infection decreased over the domestication gradient (Jaiswal et al. 2020), which can be attributed to the reduced level and inducibility of constitutive chemical defenses against pathogens (Moreira et al. 2018). Therefore, wild germplasm is often used for identifying novel sources of resistances against diverse pathogens. In fact, disease-resistance genes against leaf mold fungus and yellow leaf curl virus have been identified from the wild SP and backcrossed in modern tomato (Kruijt et al. 2004, Verlaan et al. 2013). Examples of contributions of wild germplasm in conferring resistance against various bacterial and fungal diseases in perennial crops have also been reviewed (Migicovsky and Myles 2017).

Novel beneficial mutations in wild germplasm that contributes to the enhanced expression of adaptive traits have also been left out during the domestication process. Singh et al. (2019) found novel alleles from wild plants that were associated with the increased taproot length and several basal root characteristics during common bean domestication. These root phenotypes have an important role in nutrient acquisition and drought adaptation. In wheat, a targeted evaluation of introgression lines carrying wild genome segments showed improved drought adaptation by increasing higher root:shoot biomass and better carbon assimilation levels (Placido et al. 2013). A co-expression analysis identified unique alleles associated with these wild translocation lines that regulate lateral root growth through the brassinosteroid signaling pathway (Placido et al. 2013). These wild alleles were most likely left behind due to their insignificance for adaptations to new habitats during the domestication process.

Reduced effective recombination and LD decay

There are contrasting theories explaining the changes in recombination frequencies across genomes during domestication (Ross-Ibarra 2004). The first theory proposes that strong artificial selection caused an increased recombination frequency in

accessions that underwent domestication (Rees and Dale 1974, Otto and Barton 2001). A contrasting theory proposes that higher recombination exists in wild than in the domesticated populations (Gornall 1983). An empirical analysis of chiasmata frequencies supports the hypothesis of increased recombination during plant domestication (Ross-Ibarra 2004). However, the act of strong selection creates obvious homogeneous genomes that result in reduced effective recombination events in the domesticated plants (Wright et al. 2005, Moyers et al. 2018). Moreover, since recombination reduces linkage disequilibrium (LD), an increase in the recombination frequency must cause LD to decay over shorter genomic intervals. An analysis of LD using genome-wide polymorphisms showed contrasting patterns where domesticated plants showed lower LD decay than the wild populations (Lin et al. 2014, Zhou et al. 2015). The reduced LD decay in the domesticated populations is likely driven by reduced effective population size, loss of genetic diversity and increased homozygosity across genomes on short evolutionary time scales. The latter effects are more prominent across the loci under artificial selection. The extended LD across selected loci can have negative implications too, such as those demonstrated by genetic hitchhiking of undesirable metabolites along with the selection of beneficial fruit weight alleles in tomato (Zhu et al. 2018). Furthermore, reduced effective recombination across these haplotypes can make it difficult to remove undesirable mutations through selection.

To establish the link between selection and recombination, it is also important to clarify the frequency and distribution of recombination across genomes—especially since it depends on multiple factors including the genome structure (Stapley et al. 2017). In barley and tomato, regional differences in recombination rates have also been observed during domestication (Dreissig et al. 2019, Fuentes et al. 2021). The recombination hotspots shift toward distal chromosome regions in the domesticated compared to wild barley. The latter had more recombining regions in the interstitial chromosome regions (Dreissig et al. 2019). It was proposed that shifts in recombination hotspots were a consequence of selection on defense response against pathogens since they moved near disease-resistance genes. In addition, a similar comparison revealed that many genes in the euchromatic regions of tomato genomes lost their recombination hotspots after domestication especially in SLC accessions (Fuentes et al. 2021). The upstream gene promoter regions in tomato also showed lower effective recombination in SLC than in wild SP accessions.

Alleviated inbreeding depression

Inbreeding depression lowers the vigor and fitness of progeny after mating with closely related individuals. At the genetic level, both 'dominance' and 'overdominance' mechanisms have been suggested to reduce fitness in inbreds (Charlesworth and Willis 2009). Inbreeding can promote recessive deleterious alleles in the homozygous states in populations, whereas dominant alleles mask their effects in the hybrid state (Charlesworth and Willis 2009). These alleles are usually rare mutations

in natural populations. In contrast, balancing selection can maintain heterozygotes states at certain loci to maintain higher population fitness through overdominance. The latter might be true in outcrossing species with highly heterozygous genomes and in species where heterozygosity was maintained through frequent hybridizations during the domestication process.

Several domestication-related studies have investigated the deleterious mutation load across plant genomes (Zhou et al. 2017, Bosse et al. 2018, Kim et al. 2021, Lozano et al. 2021, Razifard et al. 2021). A general trend suggests that artificial selection led to an increased proportion of deleterious mutations (Liu et al. 2017, Zhou et al. 2017, Bosse et al. 2018). For instance, deleterious mutations were 5.2% more in the *Vitis vinifera* accessions than their wild progenitors (Zhou et al. 2017) and deleterious mutations were ∼3–4% higher in domesticated Asian rice accessions compared to their wild relatives (Liu et al. 2017). Similarly, early domestication of tomato in Ecuador led to higher deleterious mutations, but the trend did not sustain after final domestication in Mexico (Razifard et al. 2021). The frequency of deleterious alleles was higher in cultivated tomatoes in general (Razifard et al. 2021). A higher number of deleterious mutations were also observed in domesticated maize and sunflower genomes (Renaut and Rieseberg 2015, Lozano et al. 2021). On the other hand, a reduction in deleterious alleles in domesticated accessions has only been observed in sorghum and soybean (Kim et al. 2021, Lozano et al. 2021), which was attributed to selfing as the primary mode of reproduction in these species (Kim et al. 2021).

Along with selection, demographic factors influencing effective population size (Ne) have also been associated with an excess deleterious mutational load during domestication (Wang et al. 2017, Gaut et al. 2018). For example, genetic drift due to reduced Ne was associated with an increase in deleterious alleles in domesticated maize (Wang et al. 2017). Gaut et al. (2018) illustrates that decreased Ne can remove slightly deleterious variants due to a population bottleneck. However, when the selection is less efficient, deleterious mutations remain and their frequency increases in domesticated populations due to genetic drift (Gaut et al. 2018, Moyers et al. 2018). These differences could be highly significant under a recessive genetic model, where heterozygous mutations contribute less to the reduced fitness. In contrast, the additive nature of mutations in outcrossing species can stabilize the number of deleterious mutations between the wild and domesticated populations (Gaut et al. 2018).

Nevertheless, the higher genetic load in several domesticated plant genomes can certainly affect the extent of inbreeding depression. This was demonstrated by a recent evaluation of inbreeding and outcrossing effects on 18 traits in landrace maize and wild teosinte populations (Samayoa et al. 2021). The results showed that inbreeding depression was higher in 15 out of 18 traits in maize landraces than in the teosinte populations, which was genetically defined by multiple small-effect and rare large-effect mutations. The highly polygenic control of inbreeding

depression makes the elimination of small-effect mutations less likely by selection bottleneck. However, some of the large-effect deleterious variants might have been lost in maize (Samayoa et al. 2021). Still, a tight linkage with desirable alleles can hinder the purging of deleterious alleles in the domesticated populations, which can only be identified and removed through high-resolution genetic analyses of the targeted loci.

Genetic Control of Indirect Phenotypic Consequences

Antagonistic pleiotropic effects

Mapping genomic regions for domesticated traits often revealed that a single QTL determines the phenotypic expression of multiple traits (Grandillo and Tanksley 1996, Singh et al. 2019). These clustering patterns of domesticated traits appear to be conserved across species, especially in Solanaceae crops including tomato, potato and pepper (Doganlar et al. 2002, Frary et al. 2003). At the genetic level, two mechanisms could explain these findings: a close genetic linkage of genes controlling individual traits or pleiotropic effects from a single gene that synchronously controls the phenotypic expression of multiple traits. Molecular cloning of several domesticated gene targets revealed them as transcriptional factors with pleiotropic effects. For example, cis-regulatory regions upstream to the *teosinte branched1* (*tb1*) domestication gene confer pleiotropic effects on plant, inflorescence and ear architecture, and root traits (Clark et al. 2006, Gaudin et al. 2014). The *tb1* gene confers these effects by regulating a transcriptional network of the core cell cycle and plant and inflorescence architectural genes including the members of MADS-box genes—many of which had selection signatures during maize domestication (Studer et al. 2017). The regulation of domesticated phenotypes through cis-regulatory elements has been suggested as a common phenomenon (Swinnen et al. 2016). However, these large-effect mutations could cause detrimental pleiotropic effects, especially if the associated genes represent the core of the transcriptional network and can likely target many other gene regulators associated with co-regulated phenotypes (Swinnen et al. 2016, Studer et al. 2017).

The Golden2-like (GLK) transcription factor associated with uniform ripening mutation (*u*) clearly demonstrates antagonistic pleiotropy during tomato domestication (Powell et al. 2012). Tomato *u* mutants lack the wild-type dark green-shoulder phenotype at the mature green stage due to the reduced number of chloroplasts and thylakoid grana—a characteristic phenotype of *GLK* transcription factors (Powell et al. 2012, Nguyen et al. 2014, Lupi et al. 2019). The tomato genome carries two *GLK* copies, *SlGLK1* and *SlGLK2*, with tissue-specific expression patterns. Out of these, *SlGLK2* is expressed in the fruit pedicel region and causes the green-shoulder phenotype (Powell et al. 2012). Positional cloning identified a non-functional allele of *SlGLK2* that was responsible for the loss of the green

shoulder phenotype (Powell et al. 2012, Nguyen et al. 2014). Artificial selection of *u* pleiotropically altered the phenotypic expression of different traits, thereby compromising the fruit quality. An analysis of mutant and overexpression lines indicated that *SlGLK2* altered the chlorophyll and starch content in mature green fruits (Powell et al. 2012) and led to an increase in sugar, total soluble solid and carotenoid content in ripe tomato fruits (Powell et al. 2012, Nguyen et al. 2014, Lupi et al. 2019). These observations suggest that the pleiotropic effects of *SlGLK2* extend through to the regulation of sugar and carotenoid metabolic pathways. Hence, a direct selection of *u* mutation inadvertently compromised the tomato fruit quality due to pleiotropic effects originating from the SlGLK2 transcription factor.

Observations of antagonistic pleiotropy have been reported in other studies as well. For example, an ethylene biosynthesis 'ACS' gene determines the occurrence of male and female flowers on the same plants in different members of the Cucurbitaceae family (Aguado et al. 2018, Che and Zhang 2019). A mutation in the coding sequence of the watermelon '*CitACS4*' gene causes hermaphroditism on the female flowers (Ji et al. 2016). Further analysis of three F_2 watermelon populations revealed that *CitACS4* also pleiotropically regulates the development of fruit and flower organs in watermelon (Aguado et al. 2018). The *CitACS4m* allele for andromonoecious sex forms promote earlier pistillate transition and pistillate flower production, while slowing down the growth and development of petals and carpels to delay anthesis of hermaphrodite flowers. The *CitACS4m* allele also reduces the fruit set (Aguado et al. 2018). In contrast, selection of a recessive mutation for the andromonoecious sex form during melon domestication removed its negative pleiotropic effects on fruit shape (Monforte et al. 2014). In melons, the monoecious female plants are preferred over andromonoecious for hybrid F_1 seeds, but they mostly have strong association with a higher and undesirable length-to-diameter ratio in fruits (Abdelmohsin and Pitrat 2008). Using a set of near isogenic lines, this study further indicated that pleiotropic effects of a single locus caused larger ovary and fruit length in the monoecious melon lines (Abdelmohsin and Pitrat 2008).

The negative pleiotropic effects described above can help realize the phenotypic outcomes of selection through molecular interactions, structural and/or developmental balance or plant fitness. Understanding these factors can clarify the role of direct and indirect selection in regulating completely independent plant phenotypes. For instance, the *u* mutation in *SlGLK2* simultaneously altered the levels of chlorophyll, starch, sugar and carotenoids in tomato fruits without affecting its size and developmental patterns. Hence, the *u* mutation can be classified under 'Molecular-Gene Pleiotropy' (Paaby and Rockman 2013) where mutation in a single gene simultaneously regulated the function of several independent phenotypes. Similarly, independent pleiotropic effects of sex-determining factors and the maize *tb1* gene, being driven by the intricated gene

regulatory network, also classify as 'Molecular-Gene Pleiotropy'. In contrast, the antagonistic pleiotropic effects on domesticated loci can be categorized as 'Developmental Pleiotropy' or 'Selectional Pleiotropy' (Paaby and Rockman 2013). For instance, selection of seed size during common bean domestication led to indirect selection of root traits through 'Developmental Pleiotropy' (Singh et al. 2019), where acts of selection at a particular developmental stage affects the phenotypic expression of traits in the related developmental stages. Moreover, the root systems of domesticated common bean, although larger and have more branching, showed lower root apical dominance than the wild plants (Singh et al. 2019). The wild alleles were associated with higher root apical dominance, which is critical for the fitness of wild plants in soils with limited water availability—especially when plants thrive under uncertain rainwater in the wild habitats. The mutations associated with fitness, like those controlling the root apical dominance, can be classified under 'Selectional Pleiotropy'.

Hitchhiking undesirable alleles

Detailed fine mapping has shown that the domestication-related major QTLs often fractionate into multiple small-effect-linked QTLs (Haggard et al. 2013, Lemmon and Doebley 2014), which explain thats how an intense selection on a major domestication target can drag closely linked genes through the domestication bottleneck. For example, stigma excertion represents a key trait for transitioning of the allogamous wild SP forms into mostly autogamous cultivated forms in tomato. Genetic fine mapping of a stigma excertion locus *style 2.1* identified five tightly linked genes controlling style length, stamen length and anther dehiscence, representing a gene complex that determines the mating behavior in tomato (Chen and Tanksley 2004). The linkage drag could be much larger in the genome cold spots, where a low recombination frequency cannot break the linkage between the selected and dragged genes. Moreover, in these instances, selection of favorable alleles for a domesticated trait can indirectly hitchhike both desirable and/or undesirable alleles for one or more dragged traits, as illustrated by following examples.

Larger fruit weight was the primary target of artificial selection in tomato (Frary et al. 2000, Chakarbati et al. 2013), and a negative correlation exists between fruit weight and sugar content in tomato (Chetelat et al. 1995, Lecomte et al. 2004). This illustrates that increasing fruit weight during tomato domestication might have an indirect negative effect on fruit sugar content. Allometrically, lower sugar or other metabolite concentrations can be taken as a dilution effect relative to the larger fruit size. However, it could also represent a linkage between alleles for fruit weight and metabolite composition where artificial selection for desirable fruit size alleles leads to hitchhiking of the undesirable fruit quality alleles. In fact, a linkage of alleles with contrasting effects on the sugar content and fruit weight exists in tomato (Chetelat et al. 1995, Lecomte et al. 2004). A fine-mapping analysis of *fw2.1* QTL in tomato showed that antagonistic alleles for fruit weight and

fruit quality traits, total sugars, titratable acidity and soluble solids (Lecomte et al. 2004)—might explain the negative correlations between fruit size and quality. A recent detailed analysis also indicates that selection for weight altered the metabolite content of fruits during development (Zhu et al. 2018). By using a known domesticated fruit weight gene, *FW11.3* or *CSR* (Huang and van der Knaap 2011, Mu et al. 2017), a set of near isogenic lines segregating for *fw11.3* showed a significant difference in eight metabolites in tomato fruit (Zhu et al. 2018). This suggested that either linkage or pleiotropy can drive the metabolite differences during *fw11.3* selection. However, transgenic complementation of wild-type tomato with a genomic clone that carried the derived *fw11.3* allele indicates no metabolic differences between the wild and derived alleles, despite the difference in the fruit weight (Zhu et al. 2018). These results demonstrated that *CSR* was not directly altering the specific metabolites in developing tomato fruits. It was rather a close linkage of genes that resulted in the indirect selection of metabolites during the direct selection of *fw11.3* alleles during tomato domestication. These findings show the cause of negative correlations between the sugar content and fruit weight and indirect selection of undesirable alleles for fruit flavor deterioration during tomato domestication.

In fact, improvement for disease resistance often relies on wild introgressions carrying resistance or R alleles, which can impose significant deleterious effects on the fruit flavor and quality (Rick and Chetelat 1995, Luo et al. 2020). For example, negative statistical correlations exist between disease resistance and horticultural traits (Haggard et al. 2013, Naegele et al. 2013). A genetic analysis of these effects confirmed that resistance against pathogens, *Phytophthora infestans* and *Phytophthora capsica* in tomato and pepper, respectively, was linked to undesirable fruit and plant characteristics (Haggard et al. 2013, Naegele et al. 2013). Another classic example of fruit quality deterioration has been demonstrated by introgression of the scab-resistance *Rvi6* (*Vf*) allele from wild *Malus floribunda* 821 to develop resistance apple cultivars (Crosby et al. 1990, Janick 2006). The use of *Rvi6* loci led to the development of over 70 scab-resistance cultivars, but its undesirable effect on the fruit size and quality remains intact (Muranty et al. 2016, Luo et al. 2020). With multiple cycles of backcrossing and selection, the undesirable effects of *Rvi6* introgression were diluted, which suggests that the linkage between desirable resistance and undesirable fruit quality alleles can be broken to a certain extent. However, a tight linkage of genes can hinder the inclusion of wild alleles in resistance breeding of fruit crops, where fruit quality and flavor are strongly preferred over disease resistance (Luo et al. 2020). Unless the linked alleles for these traits can be dissected, it remains a challenge to incorporate disease-resistance alleles from wild to elite backgrounds without compromising the quality of fruits. In such instances, artificial selection of these traits presents a unique opportunity to identify and explore the genetic causes of such relationships and exploit them for crop improvement efforts.
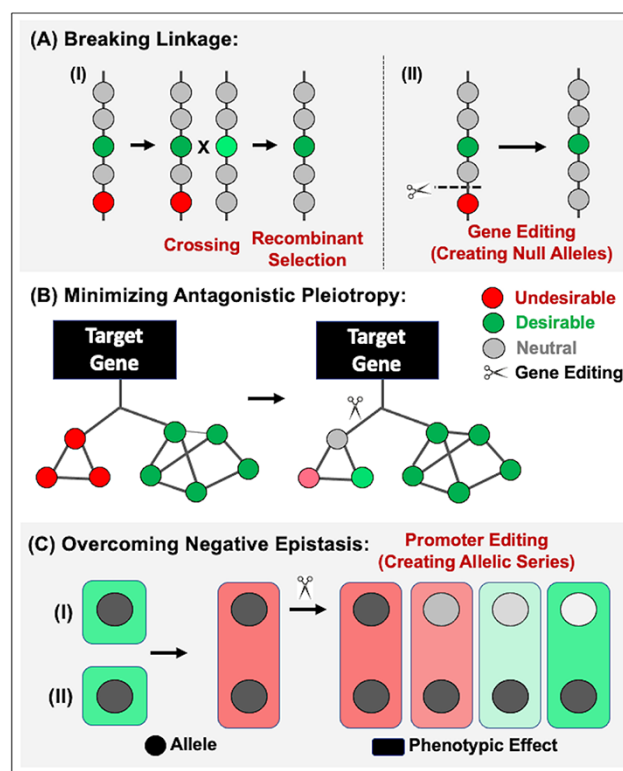
Negative epistasis

Apart from the genetic mechanisms explained above, complex gene-by-gene or epistatic interactions also limit the use of certain domesticated phenotypes (Sang 2009, Soyk et al. 2017, 2019). The epistatic interactions most likely restricted the rapid evolution of similar mutations which otherwise have been detrimental to trait expression in specific allelic combinations and must have been avoided during the domestication process. For example, mutations in *sh4* and *qSH1* loci that lead to an almost similar decrease in grain shattering were preferentially selected in different genetic backgrounds of domesticated rice (Sang 2009). Together, these mutations could have detrimental effects on grain threshing due to negative epistasis between them (Sang 2009).

A clear example of negative epistasis has been demonstrated by the selection of independent mutations for organ size and jointless fruit stems during tomato domestication (Soyk et al. 2017). Separately, these mutations lead to an increase in organ size and the removal of the fruit stem during mechanical harvesting without damaging the produce. Tomato plants carrying both of these desirable mutations exhibit low productivity due to sterility and excessive branching. Characterization of mutant plants with an excessive branching phenotype, called *compound inflorescence 2* (*s2*), showed a delay in meristem maturation during the development of early inflorescence (Soyk et al. 2017). A bulk segregant analysis of two F_2 populations generated by crossing *s2* plants with the M82 cultivar and wild SP identified two regions associated with the *s2* phenotype. A candidate gene identification and subsequent validation using loss-of-function mutations identified a pair of redundantly acting MADS-box genes that cause *s2* inflorescence branching in tomato. It appeared that negative epistasis between these two genes contributed to the undesirable branching phenotype observed during the introduction of the jointless mutation *j2* into larger fruited cultivars. The MADS-box allele, ej2^W, for enlarged leaf-like organs was selected much earlier during tomato domestication than the *j2* mutation, and the undesirable phenotypic outcome from their combination limited the utilization of jointless traits in tomato breeding and improvement (Soyk et al. 2019). Nonetheless, a complete knowledge of negative gene-to-gene interactions can help design strategies to avoid or neutralize their undesirable consequences.

Fig. 2 Mitigating undesirable effects originating from the selection of direct targets of domestication. (A) The tight linkage between desirable and undesirable genes can be broken through high-resolution fine mapping of large segregating progenies and subsequent recombinant selection (I) or by creating non-functional alleles of undesirable genes through targeted gene knockouts (II). Here, the circles represent alleles and the lines represent genome block carrying those alleles. (B) The gene-editing tools can help minimize antagonistic pleiotropic effects by creating weak alleles for undesirable genes. The intensity of the color shows the magnitude of effect. (C) The gene-editing tools can help generate allelic series that demonstrate weak to strong phenotypic effects to overcome the negative epistatic interactions through the selection of desirable combinations. Here, two independent alleles (I and II) have positive phenotypic outcomes (green rectangles), which together will produce undesirable phenotypic consequences (red rectangles) due to epistatic interactions. Promoter editing can generate allelic series (dark gray to white circles) that can help eliminate the negative epistasis between beneficial genes.

Mitigating Undesirable Effects of Plant Domestication

Using wild germplasm resources

Several approaches can be considered to eliminate the undesirable effects of plant domestication. For example, utilizing wild germplasm is a key to reintroduce the novel genetic variation that was left behind during the plant domestication process. Breeding programs often include wild crop relatives for introgression of beneficial alleles in the modern cultivars. As discussed earlier, wild alleles contributed to the enhanced expression of several useful traits associated with productivity and stress tolerance (Crosby et al. 1990, Placido et al. 2013, Migicovsky and Myles 2017). However, linkage drag of undesirable alleles can limit the use of wild germplasm for introgression of novel genes/alleles for crop improvement. In such cases, extensive recombinant screens using large segregating populations would be needed to break the tight linkage between these alleles (**Fig. 2A**). Hence, incorporating wild alleles into modern germplasm depends on the relative economic importance of the trait/s being considered for introgression. The undesirable impacts of such introgressions on primarily important

crop traits can be evaluated through subsequent trait evaluation trails under different environments. In addition, the availability of suitable wild germplasm, the cross-incompatibility between wild and domesticated plants, and the transfer of genomics approaches from domesticated to wild relatives are other challenges to consider while deploying wild resources for crop improvement (Migicovsky and Myles 2017).

Applying -omics and genome-editing approaches

The cutting edge -omics and genome-editing tools provide major opportunities to counter the undesirable consequences of plant domestication. These techniques have enabled a broader and rigorous phenotypic characterization of traits, a near complete assessment of the structure and functions of genomes and their expressed components, and a high-resolution genetic mapping to link genes to phenotypes. With the increased number of sequenced genomes, one approach would be to better annotate the QTL regions for structural and regulatory variation in order to target (or inform)the subsequent cloning of candidate genes for domestication-related traits. In addition, CRISPR/Cas-mediated gene editing can offer precise and rapid genetic improvement by modulating or generating novel phenotypic variation in plants (**Fig. 2**; Soyk et al. 2017; Li et al. 2019).

These approaches offer multiple paths to identify, dilute and eliminate the undesirable effects originating from the genetic complexities of domesticated traits (**Fig. 2**). For example, analysis of integrated genomic, transcriptomic and metabolomic datasets of several tomato genotypes elucidated previously unknown genetic effects of direct and indirect selection during tomato domestication and improvement (Zhu et al. 2018). This study highlighted that genetic linkage drove the indirect selection of undesirable flavor metabolites during selection for a larger fruit size in tomato. Once such relationships are identified, CRISPR/Cas-mediated editing can create null alleles of the genes associated with undesirable linkage drag from the direct artificial selection or introgression of wild genomes in controlled breeding experiments (**Fig. 2A**). Although this approach can facilitate the direct use of the desirable mutations in crop improvement programs without compromising other important traits, the loss-of-function coding region mutations can have pleiotropic or detrimental consequences (Li et al. 2019). In contrast, modifying the expression of original alleles by engineering cis-regulatory regions can generate more beneficial phenotypes (**Fig. 2B**, **C**). In fact, the mutations in the cis-regulatory regions were preferred during domestication to avoid deleterious pleiotropic effects from coding sequence mutations (Swinnen et al. 2016). With the use of CRISPR/Cas-mediated gene editing, a diverse array of cis-regulatory alleles with altered gene expression can be generated to achieve quantitative phenotypic variation (Soyk et al. 2017), with the subsequent selection of cis-regulatory mutations having minimal antagonistic pleiotropic effects (**Fig. 2B**). Similarly, generating cis-regulatory alleles can be particularly useful to counter negative epistatic effects between domesticated genes. For example, Soyk et al.

(2017) used natural and CRISPR/Cas-derived alleles, *j2* and *ej2*, in two MADS-box genes to overcome the negative epistatic barrier on yields during tomato domestication. The genetic interactions between these genes produced excessive inflorescence branching and sterility, but the selection of natural and CRISPR/Cas-edited mutations in heterozygous combinations, *j2 ej2^W^/+* and *j2/+ ej2^CR^*, led to weak branching and improved yields in a dosage-dependent manner (Soyk et al. 2017). With continuous improvement in -omics, high-resolution mapping and gene-editing tools, it would be worthwhile to identify such genetic interactions and resolve their subtle undesirable effects through combined natural and biotechnological solutions.

Establishing hybrid genomes

As many genomic studies have revealed, the accumulation of deleterious mutations appears to play an important role in reducing fitness during plant domestication. This was evident from the comparative analysis of selfed and outcrossed populations of maize and teosinte where inbreeding depression was higher for many traits in the former population group (Samayoa et al. 2021). In addition, the genetic architecture of inbreeding depression was highly polygenic, where most of the phenotypic variation was explained by many small-effect and few large-effect mutations. Hence, it could be challenging to weed out the undesirable effects of the deleterious mutations from the domesticated germplasm, which hinders their use in modern crop improvement programs.

Considering dominance effects as being the main driver of genetic burden, deploying hybrid breeding strategies can effectively dilute the negative effects of inbreeding depression. In this case, the effects of recessive deleterious mutations will be counteracted in the heterozygous states in hybrid individuals, which can enhance the genetic gain in the hybrid plants. For any plant species, a wider genetic base can play a critical role in selecting and deploying desirable mutations for hybrid breeding, but the selection strategies could differ in annual and perennial plants, especially when the plants are propagated through seeds or clones. Most of the annual crops are seed propagated and it requires continuous efforts to plan crossing experiments and generate hybrid progenies for cultivation. Perennial crops, however, can stay in the hybrid state forever after crossing if they continue to be clonally propagated. In fact, perennials fruit crops have retained considerable genetic variation and heterozygosity during domestication by wide hybridizations and clonal propagation (Miller and Gross 2011). Wide hybridizations promote genetic rescue by facilitating an influx of novel allelic variation from outside diverse populations (Whiteley et al. 2015), while clonal propagation can stabilize those novel alleles in heterozygous states. Incorporating and stabilizing novel alleles is critical for perennial crops to overcome the deleterious effects of recessive mutations, which is evident from their higher fitness and less inbreeding depression than the annual crops (Morgan 2001). Hence, establishing hybrid genomes, either through planned crossing experiments

or through targeted mutagenesis of genes controlling inbreeding depression, can successfully reduce the undesirable impacts of deleterious mutations in domesticated plants.

Conclusion

Insights into plant domestication have provided tremendous knowledge about the genetic control of important and complex traits. Moreover, the novel -omics and gene-editing techniques can assist in a better understanding of the complex developmental and biochemical pathways underlying these domesticated traits. A deep knowledge of these pathways can guide the development of suitable strategies to manipulate the phenotypic expression of undesirable traits for crop improvement. For example, genomics and CRISPR/Cas9 gene editing can be combined to determine the functional effects of undesirable traits and to generate quantitative variation through promoter editing and the selection of desirable quantitative phenotypes. In addition, a thorough understanding of the developmental and biochemical pathways can lead to manipulating either gene expression or enzyme active sites, that affect protein function and consequently phenotypic expression of domesticated traits.

Data Availability

No new datasets were generated or analyzed in this study.

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