

De Novo Domestication in the Multi-Omics Era

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Most cereal crops were domesticated within the last 12,000 years and subsequently spread around the world. These crops have been nourishing the world by supplying a primary energy and nutrient source, thereby playing a critical role in determining the status of human health and sustaining the global population. Here, we review the major challenges of future agriculture and emphasize the utilization of wild germplasm. De novo domestication is one of the most straightforward strategies to manipulate domestication-related and/or other genes with known function, and thereby introduce desired traits into wild plants. We also summarize known causal variations and their corresponding pathways in order to better understand the genetic basis of crop evolution, and how this knowledge could facilitate de novo domestication. Indeed knowledge-driven de novo domestication has great potential for the development of new sustainable crops that have climate-resilient high yield with low resource input and meet individual nutrient needs. Finally, we discuss current opportunities for and barriers to knowledge-driven de novo domestication.

Keywords: Agriculture challenges • De novo domestication
• Multi-omics

Introduction

Agriculture is one of the most important developments during the history of human civilization. It has tremendous implications on the world population size and human health status. Over the history of cultivation, the world food production system has been sustained by improving germplasms, extending arable land and developing agronomy systems with intensive resource input (Fig. 1A). The world's population is currently nourished by dozens of crops, which were domesticated within the past 12,000 years and supply 70% of the calories for humans (Doebley et al. 2006, Fernie and Yan 2019). The golden age of crop domestication ranged from approximately 8000 to 3000 BC, and this period has become known as the Neolithic Agricultural Revolution (Taiz 2013, Tian et al. 2021). During this stage, the dramatic selection of agronomic characteristics of wild species turned them into staple crops and led to the

switch in human lifestyle from hunter–gatherer to farmer. Supported by domesticated crops and their corresponding cultivation systems, the introduction of agriculture vastly increased food production and resulted in an initial burgeoning of the global population (Fig. 1A). Throughout history, each agricultural revolution led to subsequent rapid growth of the human population. The Hydro-Agricultural Revolution beginning in around 3000 BC is a classic example of this, in that it fed the increasing population by increasing the input of fresh water to extend the available cropland (Fig. 1A) (Taiz 2013). The expansion of arable land was then accelerated in the Medieval and Modern Agricultural Revolution that began around 1000 AD. Especially after the Industrial Revolution (1760 AD), the range of human activities was largely increased, while the production systems and techniques in agriculture were improved, leading to a rapid population growth. (Fig. 1A) (Taiz 2013, Tian et al. 2021). This expansion of cropland turned half of the available habitable land to agricultural land (Fig. 1B); however, it proved unsustainable, and was halted before the 1960s (Fig. 1A). Indeed, the most recent growth of the global population was due to the first green revolution (in the 1960s). This was achieved by the introduction of semi-dwarf genes to rice and wheat elite lines, as well as intensive resource input including fresh water, pesticides and fertilizer (Fig. 1A) (Pingali 2012, Bailey-Serres et al. 2019). By means of these revolutions, the world agricultural system has so far kept pace with global food demand; however, this has occurred in an unsustainable and environment-unfriendly manner (Pingali 2012, Steffen et al. 2015). On the one hand, this high input and output planting paradigm has become a major driver of environmental deterioration land-use competition, and fresh water and energy depletion (Steffen et al. 2015, Bailey-Serres et al. 2019, Tian et al. 2021, Yu and Li 2021). On the other hand, it is estimated that 9.2–10.4% of people are undernourished (<https://www.fao.org/>). Indeed, it will be highly difficult to nourish 10 billion people by 2050 since that will require at least a 60% increase in world crop yields (Ray et al. 2013, Springmann et al. 2018, Hickey et al. 2019). In addition to the traditional goal of stabilizing and ultimately increasing the world food supply, the global diet is shifting from vegetarian to omnivorous, which results in a rising concern regarding protein security (Tilman and Clark 2014, X. Li et al. 2020).

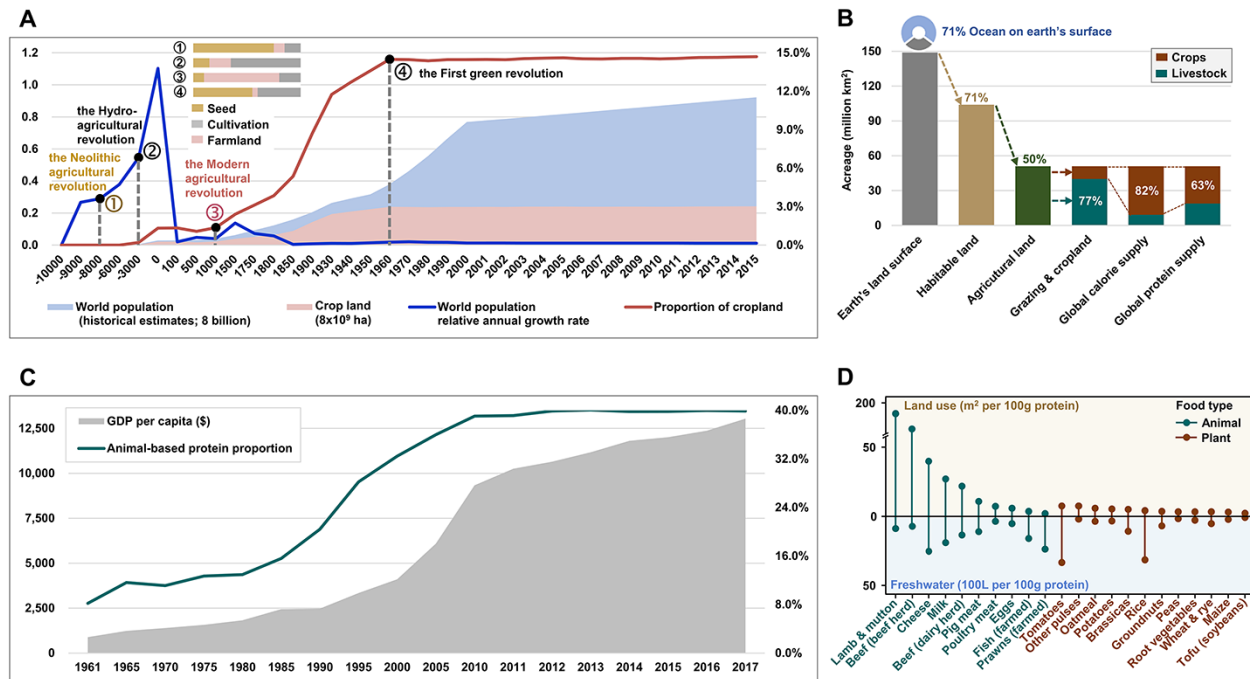


Fig. 1 Changes in agriculture systems. (A) Three pillars of agricultural systems and their relative contributions (bar diagram) at different stages (Taiz 2013, Tian et al. 2021). Seed (tan bar), cultivation (gray bar) and farmland/cropland (light red bar) played a relatively important role in four distinct revolutions, which are represented by the respective proportion of the bars. (B) Land use on the Earth (by 2000 AD). A total of 71% of the Earth's surface is covered by the ocean. With the exception of regions covered by glaciers and barren land such as deserts, beaches and regions that are exposed to rocks, there is 71% of habitable land, with half of it occupied by agriculture. In detail, livestock (meat and dairy) take up over three times more land than crops but provide only 18% of calories and 37% of proteins. (C) The requirements of animal-based food are ever increasing, which is positively correlated with the increase in GDP per capita (represented by data from China). (D) It takes more land and fresh water resources to produce animal-derived food than for vegetable-derived food. All the original data were obtained from <https://ourworldindata.org/>.

Crop breeding is the most direct and essential way in which to improve food production. In general, genetic improvement of an elite crop variety involves the selection and combination of different favorable agronomically important traits that are usually complex traits controlled by several quantitative trait loci (QTLs) (Liang et al. 2021). Limited by a poor understanding of the genetic basis of agronomic characteristics, for nearly 10,000 years crop improvement has mainly relied on observations of exterior characteristics (phenotype) (Hickey et al. 2019, Liu et al. 2021). In the past two centuries, however, crop improvement has shifted from empirical selection to knowledge- and biotechnology-based selection, which ensures the employment of favorable alleles of the target gene (Wallace et al. 2018, Fernie and Yan 2019, Hickey et al. 2019, Gao 2021, Liu et al. 2021). Breakthroughs in genetics have demonstrated that the nature of crop improvement is to find or even create novel genetic variations and achieve their desired combinations. Therefore, the efficiency of genetic improvement is mainly dependent on genetic diversity, knowledge of the genotype–phenotype links of agronomically important traits and on biotechnological approaches that allow genome shuffling for the introduction of desired traits (Gao 2021, Liang et al. 2021, Liu et al. 2021). Compared with their wild progenitors, the genetic diversity of modern cultivars is usually diminished,

which greatly limits the starting gene/allele pool for selection (Schreiber et al. 2018, Zhang and Batley 2020, Chen et al. 2021). To some extent, this reduction in diversity could be overcome by reutilizing wild relatives (Burgarella et al. 2019, Fernie and Yan 2019, Zhang and Batley 2020) since there are >7,000 semi-cultivated plant species that could serve as starting material for breeding climate-resilient crops (Smýkal et al. 2018, Zhang and Batley 2020). In the last three decades (1993–2020), causal genes underlying 364 QTLs have been cloned in maize, rice, wheat, barley, soybean and tomato (Liang et al. 2021). The natural variations and mechanisms of these causal genes provide the foundation for customized breeding. In addition, the predictability and operability of crop breeding have also been enhanced by genomics-based selection tools, such as marker-assisted selection (MAS) and genomic selection (GS) (Liang et al. 2021, Liu et al. 2021). Benefiting from recent advances in genome editing technologies, crop improvement is likely to be greatly accelerated by these efficient and precise genetic manipulation tools (Chen et al. 2019, Gao 2021).

Here, we review the unprecedented challenges that threaten future global food security and emphasize the urgent demand for breeding novel crops which are suitable for sustainable agriculture in a highly variable climate. To breed climate-resilient

varieties, vastly distributed wild plants present a great opportunity since they already inhabit diverse climatic niches (Zhang and Batley 2020). These wild species could thus be utilized via *de novo* domestication, i.e. the introduction of desired and domesticated genes into wild plants (Fernie and Yan 2019). We provide refined insights into the genetic and molecular basis of crop domestication and improvement. Moreover, we provide an overview of the dramatic innovations in breeding strategies, including advances in genomic and other -omics technologies, as well as genetic manipulation tools. We highlight the prospects of knowledge-driven *de novo* domestication supported by multi-omics tools and discuss how this emerging breeding strategy could be applied to cope with future challenges.

Challenges in Future Sustainable Agriculture

So far, four dramatic innovations of agriculture had achieved a profound crop yield increase to nourish the increasing global population (Fig. 1A) (Taiz 2013, Wallace et al. 2018, Fernie and Yan 2019, Hickey et al. 2019, Tian et al. 2021). These were accomplished by the selection of elite varieties, expansion of arable land and development of agronomy systems, including intensification of field management and extensive application of fertilizers, fresh water and pesticides (Taiz 2013, Bailey-Serres et al. 2019, Tian et al. 2021). However, the high-input and high-output mode of agriculture is becoming progressively unsustainable due to the accumulating damage to the environment caused by pollution (water eutrophication), land and fresh water erosion, biodiversity loss, and climate change driven by deforestation and associated greenhouse gas emissions (Friedlingstein et al. 2010, Taiz 2013, Steffen et al. 2015, Massawe et al. 2016). In turn, the increasing climate variability resulting from global warming has become one of the major threats to food production (Bailey-Serres et al. 2019, Cai et al. 2020, Coumou and Robinson 2013). Despite environmental damage, another difficult challenge is how to address the caloric demands of an ever-increasing world population (Gerland et al. 2014, Springmann et al. 2018, Tian et al. 2021). Thus, it is of great importance to ensure the balance between increasing human needs and the scarcity of natural resources (Bailey-Serres et al. 2019, Yu and Li 2021), such as fresh water (König et al. 2013) and arable land. Initially, 71% of the Earth's land surface was habitable land covered by forests, shrubbery and grassland. During the last few centuries, and especially after the Industrial Revolution habitable lands have been continuously squeezed out by farmland expansion. By the year 2000, 50% of habitable land had been turned into agricultural land (Fig. 1A, B), resulting in anthropogenic climate change and the decline of biodiversity (Foley et al. 2005, Friedlingstein et al. 2010, Steffen et al. 2015). Consequently, it is no longer possible to extensively improve food production by agricultural land expansion, particularly in light of the degradation of arable land due to urbanization, soil erosion and desertification (Zabel et al. 2014). In summary,

future food security faces the challenges brought about by a tough conflict between continuous population growth, dwindling farmlands and a fickle climate.

Besides increasing calorific needs, protein malnutrition is becoming another critical focus of food security (Godfray et al. 2010, Tilman and Clark 2014, Xu et al. 2021). Due to higher incomes and increased urbanization, traditional diets have shifted from cereals and vegetables to a richer omnivorous diet. However, this omnivorous diet requires much more refined fats, meats, sugars and oils (Fig. 1C) (Tilman and Clark 2014). The food-to-protein conversion efficiency is estimated to be 3% (beef) to 17% (dairy and eggs), with a quite low average conversion efficiency of 8% (Shepon et al. 2016). Due to this low conversion efficiency, the growing demand for animal-based food is aggravating the burden on the environment and agriculture since much more arable land and fresh water are required (Fig. 1B, D) (Kastner et al. 2012, Shepon et al. 2016, Bessada et al. 2019, Xu et al. 2021). For example, it takes about 84 times the amount of land to produce 100 g of protein from lamb and mutton compared with tofu (soybean) (Fig. 1D) (<https://ourworldindata.org/>). However, what makes animal-derived protein indispensable is that some essential amino acids cannot be found in plants, such as methionine (lacking in soybean), lysine and tryptophan (deficient in maize) (Galili et al. 2016, Le et al. 2016). Accompanied by socioeconomic progression, dietary patterns are remarkably variable across the world, which also represents a risk for nutritional, and particularly protein, security (Yin et al. 2015, Xu et al. 2021). Indeed, protein malnutrition is becoming an extremely severe public health concern in developing regions, such as China (Yin et al. 2015) and Africa (Xu et al. 2021). In the future, protein security will continue to be an important aspect of food security that simply cannot be ignored (Tilman and Clark 2014, Yin et al. 2015, Shepon et al. 2016, X. Li et al. 2020, Xu et al. 2021).

Taken together, these unprecedented threats impose tough challenges for crop breeding. In addition to pursuing enhanced yield, there are four emerging tasks for future sustainable agriculture (Bailey-Serres et al. 2019, Fernie and Yan 2019, Yu and Li 2021): (i) to avoid the reductions in crop production caused by extreme weather conditions, such as extreme high/low temperatures, floods and drought, (ii) to mitigate the side effects of agriculture on the environment—new environmentally friendly crop varieties would need to have an optimized combination of genetic variants which makes them more efficient in utilizing water and fertilizer, boosting photosynthesis, and thereby decreasing the burdens placed on the environment, (iii) to meet the shortage of arable land—this may be bypassed via the development of indoor vertical farming (Eshed and Lippman 2019, Fernie and Yan 2020, O'Sullivan et al. 2020)—and improve low nutrient soils which are not suitable for current crops (Osterberg et al. 2017), and (iv) to enhance the taste and levels of micronutrients. In brief, future crops need to become 'smarter' (Yu and Li 2021), namely more sustainable, nutritious and tolerant to biotic and abiotic stress.

Insights into Crop Domestication and Improvement

The methodology of crop breeding: from empirical phenotype-based selection to knowledge-driven design

Crop domestication started approximately 12,000 years ago. It has been described as a co-evolutionary process between humans and plants that resulted in natural wild plants being transformed into elite cultivars (Doebley et al. 2006, Purugganan 2019). People selected phenotypic changes, such as plant architecture, shattering, and seed color, in a dramatic manner to meet human needs (Doebley et al. 2006, Fernie and Yan 2019). The major crops feeding the world today were domesticated during the period from around 8000 BC to 3000 BC, at which point human civilization transitioned from a hunter–gatherer to an agricultural civilization (Taiz 2013, Purugganan 2019). In the subsequent thousands of years, the collected germplasms were improved through phenotype-based selection that mainly relied on the observation of exterior appearance, such as seed/fruit size and plant architecture (Wallace et al. 2018, Hickey et al. 2019). Taking advantages of genetics, it was clear that artificial selection and the shuffling of natural alleles were the foundations for the exterior phenotypic changes (Liang et al. 2021). Since plant breeding is fundamentally relied upon as a source of genetic variations, the scope of genetic variations remains an ultimate limitation in crop evolution. In the past 260 years, many innovative technologies have contributed to the artificial creation of genetic variations and the precise pyramiding of favorable alleles for desired traits. The history of crop improvement can be divided into four phases based on the revolution brought about by the various breeding methods (Wallace et al. 2018, Fernie and Yan 2019, Hickey et al. 2019, Gao 2021): (i) at the cross-breeding stage (from approximately 1760 to date), the mating of plants began to be artificially controlled. In cross-breeding, it takes about 8–10 years to generate elite cultivars (Chen et al. 2019, Gao 2021). In this way, genetic improvement is basically dependent on the limited genetic variations from two or a few parents; (ii) at the mutational breeding stage (from approximately 1928 to date), the limitation of the natural variation pool was greatly expanded by the use of randomly generated mutations via radiation and chemical mutagenesis (Fernie et al. 2006, Holme et al. 2019, Liang et al. 2021). However, these mutations are usually deleterious, and it is time consuming (taking >10 years) to map the functional mutations and introduce them into various germplasm (Holme et al. 2019, Gao 2021); (iii) during the transgenic breeding stage (from approximately 1990 to date), targeted traits could be obtained through directly integrating foreign DNA segments into the genome (Raman 2017, Holme et al. 2019). However, the applications of transgenic crops are restricted due to public concerns and strict regulatory requirements; (iv) at the genome editing breeding stage (from 2013 to date), the breadth and precision of genetic modification have been greatly improved by genome editing tools

based on CRISPR/Cas [clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein] families (Chen et al. 2019, Gao 2021). Without the requirement for backcrossing, this approach reduces the trait introduction cycle down to around 2–5 years. These recently developed genome editing tools allow precise *de novo* design of variations lacking in the natural populations. Indeed, the scope of artificial variation is infinitely expanded by the available genome editing and synthetic biology technologies (Liang et al. 2021). The next generation of breeding waves are setting off through these precise and predictable genetic engineering technologies—called design breeding (Gao 2021, Liang et al. 2021).

The combination of traits is determined by the scope of genetic variations, while the speed of breeding is dependent on the efficiency of artificial selection (Hickey et al. 2019, Liu et al. 2021). Collective evidence suggests that crop domestication began with incidental selection. Based on observations of plant phenotypes, local farmers took >20 generations to dramatically change the appearance of wild plants (Wallace et al. 2018, Fernie and Yan 2019). During the subsequent several thousand years, crops were improved mainly relying on this empirical phenotype-based selection. In the last three decades, benefiting from the revealed genetic basis of agronomically important traits, DNA-based molecular markers started to be used to assist with selection (Wallace et al. 2018, Liang et al. 2021). Exemplified by MAS and GS, this knowledge-based genotype-guided selection allows direct pyramiding of functional alleles that provide the desired properties (Liu et al. 2021). As a vital complement of phenotypic data, these genomic data and molecular markers improve the accuracy and efficiency of selection and shorten the breeding cycle. The high-throughput sequencing platforms enable the generation of large amounts of genotype data and the high-throughput phenotyping platforms allow automatic phenotypic evaluation of much larger populations from multiple layers (Yang et al. 2020), which could greatly facilitate the application of big data in the selection of elite germplasms.

The systematic changes of crop domestication: the cost of domestication and the loss of modern crop populations

During the crop evolutionary processes, domesticated genomes accumulated deleterious variations due to linkage drag and a reduced effective population size (N_e), which increased the genetic load and effectively represents the ‘cost of domestication’ (Zamir 2001, Moyers et al. 2018, Purugganan 2019, Chen et al. 2021). Consequently, most crops contain more deleterious mutations than their wild progenitors (Moyers et al. 2018, Purugganan 2019, Chen et al. 2021). Furthermore, the degree of deleterious allele enrichment is highly variable among species. For instance, maize and rice contain 10–30% and 3–4% more deleterious variants than their wild progenitors, respectively (Chen et al. 2021).

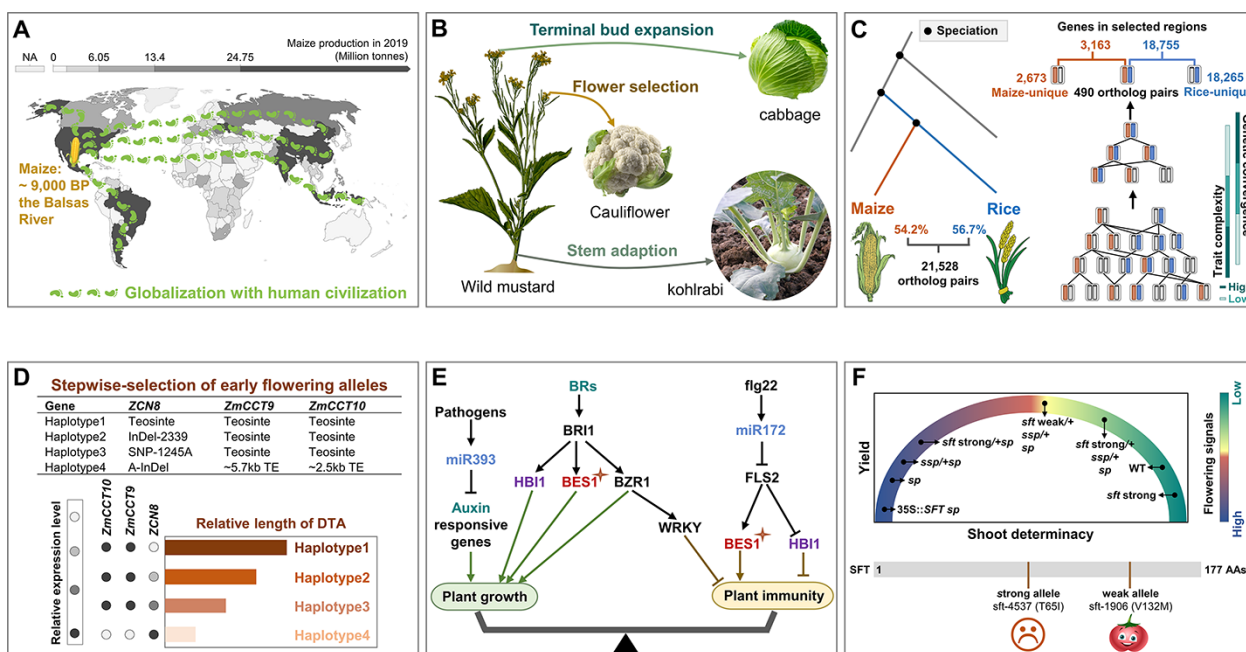


Fig. 2 Knowledge from crop breeding. (A) Maize was domesticated around the Balsas River at 9,000 years before present (BP) (Matsuoka et al. 2002) and then globalized with human civilization. Maize production from different areas is shown on the world map (modified from <https://our-world-in-data.org/>). (B, C) Wild plants maintain the potential to be domesticated in a distinct direction, which has been proven both at the phenotypic (Fernie and Yan 2019) (B) and genotypic levels (Chen et al. 2021) (C). The 21,528 maize–rice orthologs cover more than half of the number of genes in their genome individually (left) (Schnable et al. 2012, Gaut 2015), while 490 (2.3%) ortholog pairs performed convergent selection during the domestication process of both maize and rice, representing a limited number of selected genes in these species (15.5%, 490/3163 and 2.6%, 490/18,755, respectively) (upper right) (Chen et al. 2022). This can be partially explained by the association between the relative degree of trait complexity and the degree of genetic convergence during crop domestication (lower right, modified from Chen et al. (2021)). (D) Trait optimization through accumulation of favorable allelic variations among and between genes, exemplified by the shortening of maize days to anthesis (DTA) with the flowering genes (Liang et al. 2021). (E, F) Trade-off between different traits through fine-tuning of a single pleiotropic gene or altering multiple genes. The asterisk highlights the potential targets to balance plant growth and immunity (Ning et al. 2017, Wang et al. 2021) (E). The desirable *sft* weak allele is induced by chemical mutation, which does not exist in the tomato natural population (Park et al. 2014) (F).

For crop breeding, deleterious allele accumulation and a decline in genetic diversity are the two main limitations of modern cultivars compared with their wild relatives (Doebley et al. 2006, Purugganan and Fuller 2009, Purugganan 2019, Zhang and Batley 2020, Chen et al. 2021). Hence, wild plants, containing but not limited to these wild relatives, would be of great value to overcome these limitations. It is estimated that >400,000 plant species presently exist on Earth. However, only 150 plants are commonly cultivated, while 2,500 species may be regarded as fully domesticated and 7,000 species are considered semi-cultivated (Smýkal et al. 2018, Fernie and Yan 2019, Hufford et al. 2019). A total of 70% of all calories ingested in the human diet are provided by only 0.004% (15/400,000) of plant species (Smýkal et al. 2018, Fernie and Yan 2019). This scarcity of crop biodiversity was caused by a triad of factors, namely human actions, the plants themselves and the environment (Hufford et al. 2019). To some extent, our ancestors started crop domestication via unconscious selection and cultivation, based on the simple demand for living (Hufford et al. 2019, Purugganan 2019). Such simple choices turned a series

of wild plants into staple crops, including root, tuber, cereal and leguminous species (Taiz 2013). Both genetic and archaeological research has revealed that most modern crops were initially domesticated at independent domestication centers (Doebley et al. 2006, Purugganan and Fuller 2009) and subsequently dispersed across the world following the footprint of human civilization (Taiz 2013, Fernie and Yan 2019, Hufford et al. 2019). The major cereal crop maize (*Zea mays* ssp. *mays*) provides a good example for this theory. Approximately 9,000 years ago, maize was domesticated from the *Z. mays* ssp. *parviglumis* subgroup of teosinte near the Balsas River of southwest Mexico (Matsuoka et al. 2002). Nowadays, the main planting area of maize is not only limited to its original center but it is also globally distributed with the globalization of humanity (Fig. 2A) (Doebley et al. 2006, J. Liu et al. 2020). Additionally, some land that was previously used to grow macronutrient-rich fruit and vegetables is now hosting cereal crops that are rich in calories as part of the long-term pursuit of grain productivity (Herrero et al. 2017). Such transitions lead to a shrinkage in crop species diversity and thereby increase the insecurity

of food and nutrition (Herrero et al. 2017, Bailey-Serres et al. 2019).

Despite the reduction of species diversity, the genetic diversity of modern crop populations was also commonly diminished compared with their wild relatives (Hufford et al. 2019, Chen et al. 2021). This loss of diversity was caused by the decreased effective population size and the duration of domestication, which is often referred to as the 'genetic bottleneck' (Doebley et al. 2006). Notably, the extent of the genetic bottleneck suffered by different crops is not equal. For instance, maize still retained about 81% of the diversity of its wild ancestor (Hufford et al. 2012). Rice, however, went through a much more severe genetic bottleneck than maize, losing over half of the genetic diversity found in wild rice (Huang et al. 2010, Huang et al. 2012, Cubry et al. 2018). The difference between species is also supported by cucumber (Qi et al. 2013) and tomato (Lin et al. 2014). The domestication bottleneck leads to reduced diversity in neutral genes, while the selection caused a more drastic loss of diversity (Doebley et al. 2006, Olsen and Wendel 2013, Chen et al. 2021). In maize, the selected genes account for around 2–4% of the genome (Wright et al. 2005), while the percentage is nearly triple this in rice (Huang et al. 2012).

Insights from crop domestication and improvement: on the way to multi-omics

We are witnessing a torrent of -omics data, including epigenomes, genomes, epi-transcriptomes, transcriptomes, metabolomes and proteomes, in an economically feasible manner (Li and Yan 2020). As described above, current crop cultivars lost genetic diversity and gained more deleterious mutations compared with their wild progenitors. This loss of genetic diversity is also reflected at the transcriptome level, which is indicated by the universal decrease of expression diversity in current crop populations (Schreiber et al. 2018, Liu et al. 2019, Scossa et al. 2021). Intriguingly, the gene expression level of modern crops is commonly increased with respect to that of their wild ancestors, a fact that is well represented by staple crops such as maize, cotton, soybean and rice (Hufford et al. 2012, Liu et al. 2019, Liu et al. 2021). Furthermore, alternative splicing is also a critical factor in the large-scale reprogramming of the transcriptome in maize, especially during its temperate–tropical adaption (Liu et al. 2015, Chen et al. 2018).

There is a relatively conserved change of crop domestication between species at both genomic and transcriptomic levels (Scossa et al. 2021). However, the metabolic tendencies following crop domestication are considerably more species-specific (Alseikh et al. 2021). This can be partially explained by the fact that some such species-specific metabolic changes during domestication are associated with transcription factor-mediated expression regulation (Alseikh et al. 2021). The deep restructuring of the metabolome during crop breeding usually results in sacrifices of quality traits, such as color, flavor, taste and other nutrient-associated traits (Morris and Sands 2006, Folta and Klee 2016, Alseikh et al. 2021). This provides new insights into the loss of quality and nutrient value caused by

the excessive pursuit of crop yield from the perspective of interactions between the genome, transcriptome and metabolome. In the foreseeable future, the integration of multi-omics data promises a more rapid and high-throughput mining of genetic and mechanistic knowledge of crop evolution, turning the research paradigm from a single gene to a pathway or even a network (Li and Yan 2020). In this manner, knowledge gained from long-standing crop breeding practices and the enormous amount of -omics data could be combined with different breeding methods to alternative: design a relatively predictable crop breeding strategy (Li and Yan 2020, Liu et al. 2021).

The Value of De Novo Domestication

De novo domestication: an emerging method to breed new crops through direct genetic manipulation of wild plants

Plant domestication is the genetic reshuffling process mixing natural alleles in wild plants to generate new plants to meet human demands (Doebley et al. 2006). The time span of plant domestication is a major obstacle as it generally takes >20 generations to change the phenotypes of wild crops (Fernie and Yan 2019). Another problem is the lack of functional genomic information and genetic engineering tools for wild plants. In the past three decades, dramatic innovations in multi-omics techniques, increasing availability of genetic manipulation tools and the collection of knowledge concerning crop evolution have raised the possibility of accelerating the domestication process. With these advances, de novo domestication is promising to be of great potential to introduce and/or generate the desired alleles into plants that were non- or semi-domesticated (Fernie and Yan 2019). In detail, such a manipulation of domestication genes can be further divided into two types depending on the wild receptors: (i) re-domestication of the wild relatives of existing modern crops, such as potato (Ye et al. 2018), rice (Yu et al. 2021) and tomato (Zsogon et al. 2018, T. Li et al. 2018), and (ii) de novo domestication of semi- or non-domesticated crops, such as the dryland grass *Microlaena stipoides* (Shapter et al. 2013) and the orphan crop *Physalis pruinosa* (Lemmon et al. 2018). Although the reported applications of de novo domestication are fairly few, these limited successful examples suggest that using orthologs of cloned domesticated genes in wild plants can lead to alterations to achieve mimicry of domestication (Fernie and Yan 2019). For example, the morphology of an ancestral tomato line has been remarkably changed by editing genes controlling plant architecture (SP), day-length insensitivity (SP5G), fruit size (SICLV3, SIWUS, FAS and FW2.2), fruit shape (O), fruit number (MULT) and nutritional quality consisting of the vitamin C level (SIGGP1) and the lycopene content (CycB) (Zsogon et al. 2018, T. Li et al. 2018). Furthermore, the wild *Solanaceae* plant, *Physalis pruinosa*, was also rapidly domesticated with improved vital productivity traits by mutating the orthologs of the tomato genes SP, SP5G and CLV1 (Lemmon et al. 2018). In short, diverse phenotypic changes can be rapidly accomplished in wild plants through genetic engineering of very

few loci with clear functional information (Fernie and Yan 2019, Khan et al. 2019).

The value of reutilizing wild plants: reintroducing genetic diversity discarded during crop breeding

The significant loss of genetic diversity during domestication leads to the sacrifice of manifold quality- and nutrient-associated traits (Folta and Klee 2016, Hebelstrup 2017), as well as biotic and abiotic stress-resistance traits (Burgarella et al. 2019, Zhang and Batley 2020). These lost genetic variations are imperative in crop breeding programs. This loss reduces the ability of modern cultivars to tolerate suboptimal environments or to be bred into new sustainable varieties meeting the demand for high and stable production of foods with enriched nutrition under a changing climate (Asseng et al. 2014, Bailey-Serres et al. 2019, Zhang and Batley 2020). What is more problematic than the deficiency in genetic diversity is the lack of species diversity in the existing crop populations considering that only a small number of plant species have been transformed to crops. It is estimated that only about 150 crop species are commonly cultivated to feed the world, while the number of existing edible plant species is 30,000 (Shelef et al. 2017). Approximately 7,000 species are semi-cultivated, showing broader adaptation to diverse environments globally (Shelef et al. 2017, Smýkal et al. 2018). More importantly, these semi-cultivated plants have already adapted to the local climate niche, raising the potential to promote crop diversity and agricultural resilience (Shelef et al. 2017). Hence, these wild plants provide a worthy genetic complement to modern crop populations (Burgarella et al. 2019, Zhang and Batley 2020). Compared with the main crops that are produced, transported and consumed far away from their original center, native plants allow local food production with less intensive input. This drives increasing interest in a wave of de novo domestication, with the aim of incorporating more species for local agriculture to alleviate the loss of agrobiodiversity and meet the increasing needs for biofuel (Shelef et al. 2017, Fernie and Yan 2019).

Methodologies to utilize genetic diversity from wild plants: de novo domestication as a promising strategy

Introgression breeding is a commonly applied and traditional approach, whereby gene flow progresses from wild plants to crops (Burgarella et al. 2019). This gene flow has been a staple of crop breeding for many years, leading to an improvement in yield and fitness. For example, it was proven that the combination of QTL *Gn1* (grain number) and *sd1* (plant height) led to 26% higher grain number and 18% shorter plants than the common recipient rice line, Koshihikari (Ashikari et al. 2005). Similarly, beneficial gains from introgression breeding have been reported, including yield in tomato (Gur and Zamir 2004), biotic resistance (Nelson et al. 2018), late blight disease resistance in potato (Haverkort et al. 2016), abiotic resistance such as submergence tolerance in rice (Bailey-Serres et al. 2010), and green

agricultural traits such as biological nitrification inhibition in wheat (Subbarao et al. 2021), as well as a series of other adaptive traits (Burgarella et al. 2019). During the introgression process, the basic step is to select the causal variation underlying a target trait by obtaining near-isogenic lines through continuous backcrossing, which is always constrained by the cross incompatibility between the wild donor and its recipient parent (Burgarella et al. 2019, Zhang and Batley 2020). Another concern is that it is very hard to eliminate linked deleterious mutations during introgression breeding (Burgarella et al. 2019, Fernie and Yan 2019). De novo domestication, instead, provides an alternative solution to overcome the cost of domestication and the limitation of introgression breeding through the direct editing of a few critical genes in the wild germplasm (Fernie and Yan 2019). However, there are formidable obstacles that need to be overcome for wild plants, i.e. genetic transformation and subsequent regeneration remain taxonomically restricted (Gao 2021). Fast de novo domestication processes must also be optimized for wild plant species of interest (Fernie and Yan 2019, Khan et al. 2019). Notably, it is worth pointing out that introgression breeding is still a complementary methodology for de novo crop domestication, particularly given its ability to integrate large chromosomal segments from elite germplasms into wild relatives (Fernie and Yan 2019, Zhang and Batley 2020).

De novo domestication is an emerging strategy to generate new types of crops

There is a long-term and fundamental trade-off between increasing the productivity of existing crops and incorporating more species in order to increase crop diversity (Shelef et al. 2017). De novo domestication provides an opportunity to breed novel crop varieties that can out-produce current cultivated crops on suboptimal land (Osterberg et al. 2017). For example, represented by several neglected legumes, nitrogen-fixing plants hold the potential to be domesticated as crops, offering production on low-nutrient soils with low input (Belamkar et al. 2016). Another option is to breed more perennial crops with extensive root systems, which can preserve the soil quality and be produced with less water, fertilizer and labor input compared with annual crops (DeHaan et al. 2020). Moreover, some neglected and orphan plants, such as quinoa (Vega-Galvez et al. 2010) and Amaranth (Stetter et al. 2016), also represent important genetic resources that can be used to generate novel cultivars enabling growth in agricultural environments in which most existing crops are not well suited (Hardigan et al. 2017, Hendre et al. 2019, DeHaan et al. 2020).

Obviously, to maintain the worldwide production of existing crops, newly generated crops should not be involved in the competition between agricultural land and urban land. Using land that is suboptimal for current crops is one option. Another choice is the use of an indoor system or an urban vertical farming platform (Fernie and Yan 2020). Whilst it is difficult to breed desirable varieties for urban indoor cultivation with traditional

breeding methods (Touliatos et al. 2016, Benke and Tomkins 2017), genome editing tools could be used to integrate designed traits with known causal variations (Khan et al. 2019). Taking the Solanaceous fruit tomato as an example, the triple mutant *sp/sp5g/sler* offered a compact stature for cultivating tomato in urban indoor systems without yield penalty (Kwon et al. 2020). Moreover, the orthologs of *SISP* and *SIER* in groundcherry (*Physalis pruinosa*) have been proven to have a conserved function, offering targets to create loss-of-function mutants with determinate shoot and shoot internodes that are suitable for urban farming (Kwon et al. 2020). Consequently, the crop diversity in indoor farms is widened through developing new traits in two members of the Solanaceae family (O'Sullivan et al. 2020). In addition to these mentioned genes in Solanaceae, many other genes involved in the florigen and gibberellin regulation pathways also have great potential to be manipulated to change flowering time and plant architecture in more plants, which leads to breeding more adaptive crops for indoor farm systems (Eshed and Lippman 2019).

The Knowledge Needed for De Novo Domestication

At the initial stage of crop domestication, wild plants were simply collected and planted, which led to the convergent phenotypes between independently domesticated crops, termed 'the domestication syndrome' (Doebley et al. 2006). Crop domestication syndrome includes more determinate growth, increased apical dominance, loss of seed dormancy, and shattering (Doebley et al. 2006, Purugganan 2019). Conversely, it appears that demand-oriented and experience-based selection ultimately introduced traits in a species-unique manner. For example, crop productivity improved due to seed number increments in rice (Si et al. 2016), while that of tomato and eggplants improved due to an increase of fruit size (G. Zhu et al. 2018). Another typical example of phenotypic divergence is that kohlrabi, broccoli and cabbage were selected from the stem, flower and terminal bud of wild mustard, respectively (Fig. 2B) (Fernie and Yan 2019). In summary, phenotype convergence and divergence commonly existed during crop domestication.

During plant domestication, some conserved orthologous genes were selected in a parallel manner and controlled similar traits in distinct crops (Purugganan 2019). This parallel and convergent evolution progress has been indicated by a series of genes, such as the seed dormancy gene *G* (M. Wang et al. 2018), the shattering genes *Sh1* (Lin et al. 2012) and *Btr1* (Pourkheirandish et al. 2015), the seed filling gene *SWEET4* (Sosso et al. 2015) and the grain number gene *KRN2* (Chen et al. 2022). This suggested that the phenotypic convergent changes are partially consistent with the genetically conserved evolution on a single gene level while, on a pathway or network level, the interspecies genetic convergence is dependent on the degree of

trait complexity (Fig. 2C) (Chen et al. 2021, Liang et al. 2021). As reported, there were 21,528 maize–rice orthologs, covering more than half of the number of genes in each genome (Fig. 2C) (Schnable et al. 2012, Gaut 2015). Of these orthologs, only 2.3% (490/21,528) maize–rice ortholog pairs were convergently selected in a parallel manner, only accounting for 15.5% (490/3,163) and 2.6% (490/18,755) of selected genes during maize and rice domestication (Chen et al. 2022) (Fig. 2C). These data from comparative genomics suggested that convergent phenotypic selection across species was only partly driven by conservatively selected genes during crop domestication. Actually, the limited degree of convergent interspecies selection resulted from two factors: (i) for selection of human desired traits, far less time was employed than was required for the evolutionary divergence across species, represented by maize and rice (Chen et al. 2022) and (ii) the degree of trait complexity was associated with the degree of genetic convergence, involving the complexity and convergence of gene networks regulating domestication traits (Chen et al. 2021) (Fig. 2C). Since many agronomically important traits are complex, it is not surprising that only 2.6–15.5% of genes experienced convergent selection in maize and rice evolution (Chen et al. 2022). In addition to the proportion of genes under parallel selection, the relative degree of genetic divergence in the evolution of different crops can also be represented by species-unique selected genes, including genes with or without orthologs. In some cases, the different evolutionary roles of ortholog pairs were exhibited in different ways (Chen et al. 2021). (i) The ortholog pairs were both selected but at a different evolutionary stage, represented by the selection of *Zmtga1* during the initial period of maize domestication and its ortholog *OsGW8/OsSPL16* during modern rice improvement. This type of temporally resolved functional ortholog also includes *OsIPA1/OsSPL14* (during rice improvement) and its ortholog *ZmUB3* (in both maize domestication and improvement), together with *OsLG1* (in rice domestication) and *ZmIlg1* (in maize improvement). (ii) The ortholog pairs were both selected but under dissimilar regulatory pathways. For example, *Zmtb1* directly represses the expression of *ZmUB3* in maize, while its ortholog, *OsTB1*, is activated by *OsIPA1*. The divergent genetic paths of similar traits between species have also been proved in wheat, barley, tomato and soybean breeding progress (Liang et al. 2021). Although the human needs for different crops are similar, considerable inter- or intraspecies variations were observed on both the phenotypic and genotypic level. This is consistent with the fact that crop breeding has only advanced from experience- or phenotype-based to a knowledge-driven practice over the last three decades (Liang et al. 2021, Liu et al. 2021).

Given that similar morphological and physiological changes are driven by genetically convergent evolution processes among diverse cereals, it is possible to rapidly domesticate a wild plant through manipulation of orthologs (Fernie and Yan 2019, Khan et al. 2019). The obstacles are to choose functional genes

and to edit them for the combination of desired characteristics. The limited number of domestication practices indicates that the type of genetic variations selected at the initial stage of domestication were different across species, which might mainly result from different mating systems (Chen et al. 2021, Liang et al. 2021). For instance, in maize the selection of gain-of-function, regulatory and standing variation was preferred during its domestication, while rice domestication favored loss-of-function, coding and de novo variation (Chen et al. 2021). In order to initially reproduce these domestication traits in a wild plant, recessive and loss-of-function alleles are recommended targets, as gene knock-out is relatively efficient and easy compared with gain-of-function approaches (Anzalone et al. 2020, Gao 2021). It involves, but is not limited to, the reduced expression of KRN (kernel row number)4/UB3 (Unbranched3) and *etb1.2/ZmSh1-1* in maize, as well as the functional loss of 10 (56%) QTLs in rice (Chen et al. 2021). In monocot (rice, maize, wheat and barley) and dicot crops (tomato and soybean), there are 364 cloned QTLs that have been reviewed in this context (Liang et al. 2021). This allows an unprecedented understanding of natural variations underlying vital traits in crop breeding and can serve as the core genetic resource for de novo trait creation.

It is necessary to integrate more than one genetic variation in order to accomplish the desired performance in crop breeding programs. For example, in order to adapt to the Mexican highlands, maize flowering time was brought forward through the sequential accumulation of two favorable alleles in the promoter of *ZCN8* (Fig. 2D) (Guo et al. 2018, Liang et al. 2021). This collection of diverse causative alleles in a single gene is comparatively harder than the introduction of traits controlled by individual genetic variation. A further difficult task is to harness functional alleles between genes for the optimization of beneficial traits (Park et al. 2014, Liang et al. 2021). This also could be represented by the fitness of maize for the Mexican highlands, resulting from the independent selection of *ZmRap2.7*, *ZmCCT9* and *ZmCCT10* (Fig. 2D) (Huang et al. 2018, Liang et al. 2021). Hence, genome editing strategies that target multiple sites in one step are required to pyramid favorable alleles within a single gene or across genes that regulate the same traits (Doll et al. 2019). Furthermore, gene editing tools that allow the production of de novo genetic changes are excellent tools to develop enhanced traits that do not exist in nature. For example, base-editing tools have been utilized to generate saturation mutations for improved herbicide resistance (Kuang et al. 2020, C. Li et al. 2020).

In crop breeding, linkage drag only indicates the undesired selection driven by the physical linkage of genes at the chromosomal level, which can be overcome by genome editing technologies (Gao 2021). A higher task of crop breeding, however, is to enhance distinct agronomically important traits at the same time, which is rendered extremely difficult by the interactive nature of gene networks and the presence of pleiotropic genes. For example, the difficulty in the trade-off between yield and stress resilience is explained by the molecular networks corresponding to plant growth and immunity (Fig. 2E) (Ning et al.

2017, Wang et al. 2021). On the one hand, these two traits are regulated by diverse yet interacting pathways, involving pathogens, plant hormones and microRNAs (Fig. 2E). On the other hand, increasing evidence has revealed that many genes contributing to immunity have also been employed to regulate plant growth. The transcription factor-coding gene *HBI1* is a representative of those pleiotropic genes and also a negative factor for the balance of plant yield and immunity (Fig. 2E) (Wang et al. 2021). Given these new insights into the genetic mechanism of plant yield and pathogen resilience, it is possible to improve the overall performance of these traits. For example, *BES1* allows the enhancement of plant resistance while promoting plant growth, which is a potential gene resource for breeding both high yield and disease resistance varieties (Fig. 2E) (Wang et al. 2021). These genes with the ability to balance diverse traits are hub pleiotropic genes. An alternative way to enhance crop performance overall is by regulating a single hub pleiotropic gene. For example, *TaMLO* (Song et al. 2022), *OsIPA1* (Lu et al. 2013, J. Wang et al. 2018, Song et al. 2022) and *OsSWEET* (Eom et al. 2019) provide targets to balance yield with biotic resistance, while *OsGRF4* (also known as *GS2*, *GL2* or *qGRN2*) could be utilized for sustainable crop creation due to its regulation of both nitrogen-use efficiency and yield (Che et al. 2015, Hu et al. 2015, S. Li et al. 2018). One critical barrier is to achieve fine-tuning of the hub genes for optimization of diverse traits. In tomato, productivity has been optimized by integrating different genes in the florigen pathway (Fig. 2F) (Park et al. 2014). Notably, the favorable weak allele of the florigen gene *SFT* which was screened using chemically induced mutagenesis, is absent in the tomato natural gene pool (Park et al. 2014). Recently, it was shown that the promoter deletion of *IPA1* by CRISPR/Cas9 gene editing could resolve the trade-off between grain yield and tiller number (Song et al. 2022). To design these complex traits, knowledge-based de novo domestication is thus one of the top recommended approaches.

Roadmap to Knowledge-Based De Novo Domestication in the Multi-Omics Era

Supported by the knowledge of genotype–phenotype links and by the genome editing capability of CRISPR/Cas systems, de novo domestication is a straightforward strategy to meet the next wave of crop breeding, yet it needs to be directly initiated in wild plants. Of the enormous list of wild plants that could be employed in de novo domestication, diverse wild relatives of current cultivated accessions are the most direct genetic resources. Benefiting from the functional genetic information dissected in modern crops, they hold tremendous potential to offset the erosion of genetic diversity and to regain valuable alleles (Fig. 3A, B). Those valuable alleles refer to the natural polymorphisms that confer improvement of important agronomic traits, involving upright leaf angle (Tian et al. 2019), improved yield (Fridman et al. 2004, Gur and Zamir 2004, Ashikari et al. 2005), enriched flavor (Tieman et al. 2017, G. Zhu et al. 2018), stress resistance (Bailey-Serres et al. 2010, Haverkort et al. 2016, Nelson et al. 2018) and high nitrogen-use efficiency (Subbarao

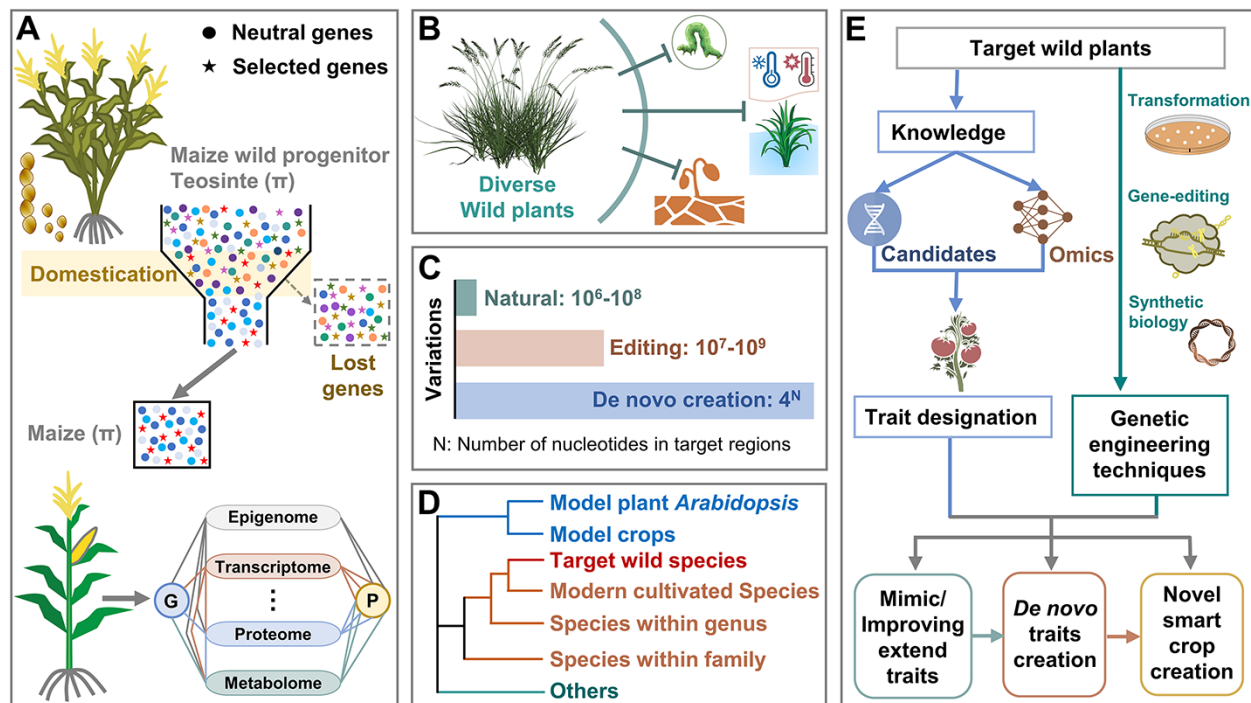


Fig. 3 Workflow and value of knowledge-driven de novo domestication. (A) The domestication and improvement of crops have resulted in the loss of genetic diversity, along with the collection of knowledge on multiple -omics levels. (B) Wild plants maintain the genetic diversity to be resistant to either biotic or abiotic stress. (C) The variation scales are estimated roughly (modified from Liang et al. (2021): natural variation is only estimated from the HapMap-like data and the number of structural variations from long-read sequencing, exemplified by pan-genome datasets of tomato (Alonge et al. 2020) and soybean (Liu et al. 2020c); editing variation is simply calculated from the number of Cas9 guide RNAs (gRNAs) (approximately $3 \times 10^6 - 1 \times 10^8$) in the genomic region, multiplied by approximately 3–25 mutations per gRNA (H.J. Liu et al. 2020). (D) Phylogenetic analysis of target genes on both the gene and protein level. (E) Workflow of knowledge-driven de novo domestication.

et al. 2021). A problem with these wild-specific alleles utilized for exotic introgression is the linkage drag of deleterious mutations, which can be overcome by genome editing-based breeding. This has been proven in the high yield tomato with balanced resistance or nutrition (Zsogon et al. 2018, T. Li et al. 2018), self-compatible diploid potato (Ye et al. 2018) and allotetraploid rice (Yu et al. 2021). In addition, to utilize these crop progenitors, orphan crops or other neglected plants provide great potential to keep pace with ongoing climate change, as local varieties have a better performance in their local climate niche (Shelef et al. 2017, Hendre et al. 2019). For example, white mustard *Sinapis alba* provides a great substitute for the biofuel crop *Brassica napus*, especially under climate change scenarios (Jaime et al. 2018). There are also alternative wild species for important tuber crops such as potato and cassava (Fernie and Yan 2019). In practice, it has been proven that the undesirable characteristics of the orphan crop groundcherry (*P. pruinosa*) could be rapidly domesticated through knock-out of the orthologs belonging to known tomato genes that control plant architecture, fruit density and fruit size (Lemmon et al. 2018). In contrast to the high input following the first green revolution, several under-utilized legumes are being revisited for domestication as high-nutritional crops that can grow and produce in low-nutrient soils with low input (Belamkar et al. 2016). Benefiting from

breakthrough techniques including genetic transformation and CRISPR/Cas9-based genome editing, a dandelion species, *Taraxacum kok-saghyz*, offers an enhanced potential to be genetically modified for rubber production (Iaffaldano et al. 2016). Taken together, wild plants with beneficial traits, genomic or other -omics data, or exhibiting genetic transformation capability were listed as candidate species for de novo domestication (Osterberg et al. 2017, Fernie and Yan 2019, Hendre et al. 2019).

The first step is primarily to gain fitness in semi-domesticated or wild plants, which will allow for artificial cultivation, transformation and regeneration. Secondly, it is imperative to start the design of new traits or novel crops by choosing favorable functional genes and the strategies to generate favorable variations, and combine them (Fig. 3). For example, the tuber-based clonal propagation of traditional tetraploid potato was shifted to diploid inbred lines with sexual reproduction by knocking out a single self-incompatible gene, *S-RNase* (Ye et al. 2018). In contrast, rice varieties are expanding from diploid to polyploid in light of their stronger vigor and better resilience when subjected to genomic or environmental variation (DeHaan et al. 2020, Yu et al. 2021). An alternative pathway to tackle the lack of energy and labor is transitioning of annual crops to perennials, which contain thriving root systems with the potential

to yield on infertile soil and, at the same time, preserve soil quality. Furthermore, Solanaceae fruit crops have been customized rapidly to suit indoor urban cultivation, which would reduce the impact of the deterioration of farmland and the unpredictable environment (Kwon et al. 2020). Unlike typical crops in which maximum yield per unit field is the goal, vertical farming provides a new sustainable cultivation destination which sacrifices yield per plant but enhances productivity with high-density planting and rapid cycling (Benke and Tomkins 2017, Li and Yan 2020, O'Sullivan et al. 2020). According to the specific breeding purpose, it is feasible to obtain -omics data of any target plant at an acceptable cost, which would assist the identification, creation and integration of functional genetic variations (Li and Yan 2020), including identification and assignment of orthologs belonging to known domesticated genes. This is one of the fundamentals of gene editing-based de novo domestication.

The scope of genetic variation remains an ultimate limitation on crop breeding. As roughly estimated from tomato (Alonge et al. 2020) and soybean (Y. Liu et al. 2020) pan-genomes, the theoretical scope of natural variation ranges from 10^6 to 10^8 , while the scope of variation generated by genome editing [Cas9 with single-guide RNA in maize (HJ. Liu et al. 2020)] is roughly 10-fold higher. However, this scope of variation can theoretically be raised to infinity with the de novo design of nucleotides (Fig. 3C) (Liang et al. 2021). Since the ability to generate genetic variation is significantly improved, the other task is to uncover the causative variations during crop evolution. Indeed, based on the functional dissection of genes, some domestication events have been reproduced by genome editing, containing *qSH1* and *sh4* (shatter resistance) (Shapter et al. 2013), *Btr1* (non-brittle rachis) (Pourkheirandish et al. 2015) and genes related to higher productivity (Park et al. 2014). Transgenic (Raman 2017) or RNA interference (Osterberg et al. 2017, Fernie and Yan 2019) approaches have been demonstrated to reproduce domestication events. However, these are accompanied by the random integration of foreign DNA in the target genome. Thus, in order to domesticate wild plants and obtain suitable editing lines for the introduction of an ideal trait, gene editing tools are preferable (Chen et al. 2019, Gao 2021). Recently, synthetic biology approaches showed their power in introducing novel traits to convert crops to satisfy diverse demands, which could be represented by enriching nutrients (Butelli et al. 2008, Beyer 2010, Q. Zhu et al. 2018, Napier et al. 2019, Han et al. 2020), improving yield by manipulating the pathways of photosynthesis (Kubis and Bar-Even 2019), photorespiration (Shen et al. 2019, South et al. 2019) or transpiration (Papanatsiou et al. 2019), and promoting rhizobium symbioses, or even producing medicinal compounds (Zhang et al. 2015, Fuentes et al. 2016). The conventional way to combine different traits is QTL pyramiding (Gur and Zamir 2004, Ashikari et al. 2005), which remains complementary to the knowledge-driven and gene editing-based de novo domestication (Fig. 3). In general, the modification of several domestication-related genes will turn the wild plants into a population that is appropriate for transformation and cultivation. Then, to obtain the ideal crop, another round of

introduction of multiple and complex traits is needed, requiring the combination of a series of causal alleles (Fig. 3C). It is worth pointing out that one major concern of de novo domestication is the limitation of 'knowledge', involving but not limited to the molecular mechanism underlying genetically non-additive genes, represented by epistasis genes (Soyk et al. 2017). At the initial stage of knowledge- and biotechnology-driven de novo domestication, we recommended combination of genes without genetic crosstalk or single pleiotropic genes, such as *IPA1* (Song et al. 2022), *GRF4* (S. Li et al. 2018), *SWEET* (Eom et al. 2019) and *MLO* (Li et al. 2022).

Perspectives

Over a long history of nearly 12,000 years, humans domesticated and improved crops (Hickey et al. 2019). Crop breeding has mainly gone through four stages (Wallace et al. 2018, Fernie and Yan 2019), by improving technologies to create and integrate genetic variations (Chen et al. 2019, Gao 2021). As learnt from the past, progress in breeding and its development are all about mining, creating and exploiting genetic variations (Chen et al. 2021, Gao 2021, Liang et al. 2021). To feed 10 billion inhabitants, present global crop productivity should be increased by 60% (Springmann et al. 2018), which requires an urgent acceleration of smart and resistant crop design, especially taking into consideration the diminishing available land and energy resources, and the acceleration of climate variation (Bailey-Serres et al. 2019, Tian et al. 2021, Yu and Li 2021). Knowledge-driven and genome editing-based de novo domestication of wild plants should be employed as a rapid way to create new crops that can grow without competing with existing arable land and current crop populations.

Detailed knowledge from model or crop plants should be transferred to target plants (Kang et al. 2016). In practice, the function of homologs has been proven to be transferred between crops and their wild ancestors or relatives (Zsogon et al. 2018, T. Li et al. 2018, Yu et al. 2021). Beyond genome editing, introgression breeding can introduce a chromosomal segment to a receptor genome. For either approach, knowledge is key. Thus, natural variations should constantly be surveyed in order to enhance the predictability or design for novel traits or crops. Cloning pleiotropic genes is important since they could ensure the trade-off between distinct traits to achieve the overall performance in the design of future crops. For example, it was demonstrated that the trade-off between tiller number and grains per panicle could be overcome by editing the *cis*-regulatory region in *IPA1* (Song et al. 2022). Another task is to resolve the crosstalk between genes, including but not limited to epistatic genes (Soyk et al. 2017). It is conceivable that this process could be accelerated by machine learning (Sartor et al. 2019), with the pan-genome or pan-family datasets probing specific species (Tao et al. 2019, Y. Liu et al. 2020).

Given their great diversity, it will be critical to tap into seed banks in a high-throughput manner. Beyond these finite natural variations, genome editing toolkits and de novo synthetic approaches have the possibility to greatly extend the

scope of genetic variation (Chen et al. 2019, Gao 2021, Liang et al. 2021). However, policy barriers and the technical challenges of transformation still represent major hurdles (Gao 2021). In practice, for either approach to de novo domestication, addressing acceptance at the social, economic, ethical and legal level is a crucial starting point (Osterberg et al. 2017).

Currently, de novo domestication is essentially restricted to introducing loss-of-function mutations into wild plants to obtain beneficial effects, exemplified by wild relatives in the rapid domestication of tomato, potato and rice, or the under-utilized orphan crop groundcherry. It generally begins with the removal of undesirable characteristics from target wild plants, such as a weeping growth habit, limited productivity or toxicity. This is not to say that traditional breeding should be replaced by genome editing-based breeding, but rather that classic or new strategies, such as high-throughput phenotyping, MAS, GS and speed breeding, should be combined to guarantee faster future breeding.

Although we have greatly emphasized the importance of crop breeding, this does not mean that agronomy is unimportant. It has recently been reported that the production of staple crops (maize, rice and wheat) in China has been increased under decreasing nitrogen fertilizer by enhanced management of smallholder farmers (Cui et al. 2018). Thus, it is critical to endow better management technologies on the 2.5 billion smallholders worldwide since they account for 60% of the global arable land. That is to say, future sustainable breeding should cooperate with agronomy to attain productivity in the absence of environmental penalties (Cui et al. 2018, Fernie and Yan 2019). Indeed, it is our belief that to exploit the full potential of elite variates, future sustainable crop populations should be designed using multi-disciplinary approaches (Bailey-Serres et al. 2019).

Data Availability

No new datasets were generated or analyzed in this study.

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