

PERSPECTIVE

Designing future crops: challenges and strategies for sustainable agriculture

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Received 7 October 2020; revised 22 November 2020; accepted 26 November 2020; published online 1 December 2020.

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SUMMARY

Crop production is facing unprecedented challenges. Despite the fact that the food supply has significantly increased over the past half-century, ~8.9 and 14.3% people are still suffering from hunger and malnutrition, respectively. Agricultural environments are continuously threatened by a booming world population, a shortage of arable land, and rapid changes in climate. To ensure food and ecosystem security, there is a need to design future crops for sustainable agriculture development by maximizing net production and minimizing undesirable effects on the environment. The future crops design projects, recently launched by the National Natural Science Foundation of China and Chinese Academy of Sciences (CAS), aim to develop a roadmap for rapid design of customized future crops using cutting-edge technologies in the Breeding 4.0 era. In this perspective, we first introduce the background and missions of these projects. We then outline strategies to design future crops, such as improvement of current well-cultivated crops, *de novo* domestication of wild species and redomestication of current cultivated crops. We further discuss how these ambitious goals can be achieved by the recent development of new integrative omics tools, advanced genome-editing tools and synthetic biology approaches. Finally, we summarize related opportunities and challenges in these projects.

Keywords: National Natural Science Foundation of China (NSFC), Strategic Priority Research Program of the Chinese Academy of Sciences, sustainable agriculture, future crops, molecular design, genome editing.

INTRODUCTION: THE VALUE OF FUTURE CROP DESIGN

Modern humans originated in Africa within the past 200 000 years. Throughout their history, humans have been looking for solutions to obtain one of the basic necessities: food. For most of their evolutionary history, humans survived as hunter-gatherers, by which means only a maximum of several million people could be supported. The invention of agriculture increased food production and led to a rapid growth in the human population, which reached 50 million by the Bronze Age, 250 million by the time of Christ, and 1 billion by the middle of the 18th century. The

growth of our population has continuously accelerated: it took 100 years for the population to grow from 1 to 2 billion (in 1927), whereas it took only another 100 years to reach 7 billion (in 2020; Figure 1a, data from <https://ourworldindata.org/>).

From the perspective of human evolution, each period of rapid population growth, such as during the Neolithic agricultural revolution, which began at about 8000 BC, the hydro agricultural or irrigation revolutions in the Near East, which began about 3000 BC, and the medieval and modern agricultural periods, which began about 1000 AD, benefited

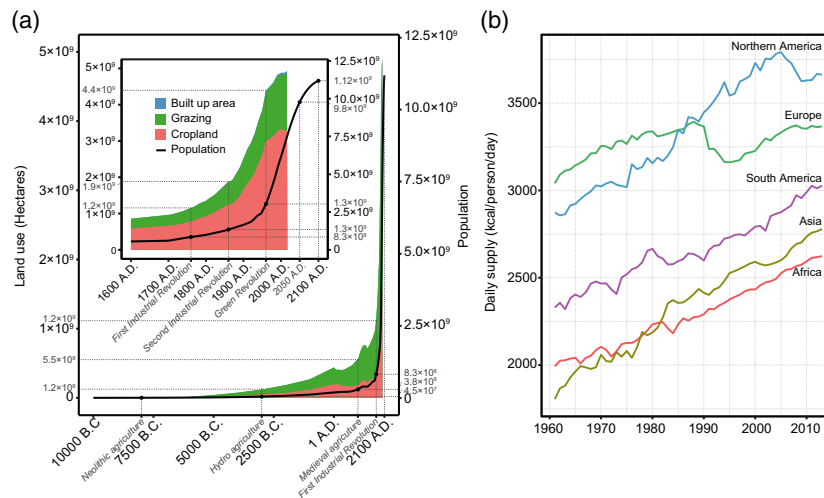


Figure 1. Trends of population growth, land use and food daily supply. (a) Population growth and land use. (b) Food daily supply. Original data were from <https://ourworldindata.org/>.

from an advance in agriculture (Taiz, 2013; Wallace *et al.*, 2018). The recent rapid population growth during the past 300 years, in contrast, mainly resulted from the Industrial Revolution, which began in Britain about 1760. The Industrial Revolution greatly increased the range of human activities and accelerated farmland expansion. In 1700, it was reported that nearly 95% of Earth's ice-free land consisted of wildlands and semi-natural anthromes; however, by 2000, ~55% of these regions were used as arable land (Figure 1a, data from <https://ourworldindata.org/>). The Industrial Revolution also gave birth to new technologies and production systems in agriculture, such as the application of larger irrigation systems, and more fertilizers and pesticides. In the 1960s, semi-dwarf wheat and rice varieties were introduced. These semi-dwarf crops exhibit beneficial characteristics, such as improved response to fertilizer input, lodging resistance and enhanced light utilization (Hedden, 2003; Wallace *et al.*, 2018). Along with the fertilizers, pesticides and irrigation systems made possible by the Industrial Revolution, semi-dwarf crops were quickly adopted and resulted in a significant increase in total grain production globally. This big leap in agriculture was known as the 'Green Revolution' (Khush, 2001). Indeed, statistical data have revealed that the average daily food supply per person (in terms of calories) has doubled since the middle of the 19th century (Figure 1b, data from <https://ourworldindata.org/>).

It is estimated that the world population will rise to more than 9 billion by 2050 (Alexandratos, 1999; Cassman, 1999), and at that time we will need at least 60% more food than is consumed by humans today. Moreover, our population will continuously increase, reaching over 11 billion by 2100 (Figure 1a, data from <https://ourworldindata.org/>). How to feed the increasing population is a challenge facing

the whole world (Tilman *et al.*, 2001; Godfray *et al.*, 2010; Foley *et al.*, 2011; Wallace *et al.*, 2018).

A simple solution to feed a population of 9 billion is to constantly turn wild habitats into farmland. However, this type of expansion is unrealistic as most of the world's ice-free and non-barren land area has been exhausted, and much of the rest is unlikely to sustain high yields (Cassman, 1999). More importantly, intact forests have been known to play essential roles in protecting the environment, such as storing fresh water, decreasing flooding and regenerating fertile soils. Clearing of forests will result in prohibitive ecological costs, such as loss of biodiversity and greenhouse gas emissions. It was reported that, due to agriculture expansion, ~30% of all plant species will become extinct (Taiz, 2013). The destruction of tropical forests releases about 1.1×10^{12} tons of carbon per year, which accounts for 12% of total anthropogenic CO₂ emissions (Friedlingstein *et al.*, 2010).

Although it has led to an increase in grain production and alleviation of food shortages, intensive agriculture, also known as intensive farming and industrial agriculture, now brings disadvantages. The high productivity of Green Revolution crops is often based on a high input of fertilizers, pesticides and fresh water. FAO (Food and Agriculture Organization of the United Nations; <http://faostat.fao.org/>) data indicate that, during the past half-century, nitrogenous, phosphate and potash fertilizer usage has increased more than 800, 300 and 125%, respectively. Meanwhile, the consumption of pesticides has increased, roughly doubling during the past 30 years (Figure 2a–c). The extensive use of chemical fertilizers and pesticides has resulted in eutrophication and habitat destruction, which in turn leads to ecosystem simplification, loss of ecosystem services and species extinctions (Tilman *et al.*, 2001).

Figure 2. Fertilizers, fresh water and pesticides usages, and environmental changes in the history.

(a) Nitrogenous, phosphate and potash fertilizers usage.

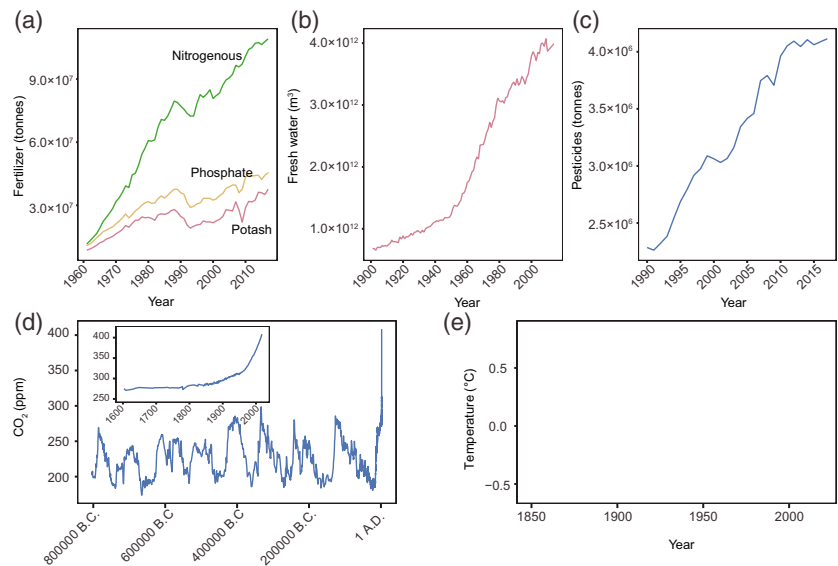
(b) Fresh water usage.

(c) Pesticides usage.

(d) CO₂ concentration changes.

(e) Global average temperature changes.

Original data for CO₂ concentration were from Met Office Hadley Centre (<https://www.metoffice.gov.uk/hadobs/hadcrut4/index.html>), and for others from Food and Agriculture Organization of the United Nations (<http://faostat.fao.org/>).



Agricultural expansion and intensification have a profound influence on our atmosphere as well. These atmospheric changes (i.e. climate change) will in turn affect global food security (Wheeler and von Braun, 2013). The CO₂ concentration remained at 250 ppm or below for a long period of time before the beginning of the 19th century. It then continuously increased to a level of ~400 ppm in 2013 (Figure 2d). Because CO₂ emissions are a major contributor to the greenhouse effect, the global average temperature has increased by more than 1°C since 1850 (Figure 2e). Notably, if not properly controlled, climate deterioration can become irreversible: an elevation of temperature leads to a higher frequency of forest fires and ice-sheet loss in the Arctic, which will subsequently cause an increase in CO₂ emissions and temperature. In particular, global warming will result in maldistribution of rainfalls, aggravating flooding and drought in some areas, and have deleterious effects on crop growth, such as a decrease in seed germination and reproduction, and an increase in plant diseases and herbivore attacks (Lobell and Gourdji, 2012; Taiz, 2013; Wheeler and von Braun, 2013).

In summary, we are facing unprecedented challenges, that is, further improving grain production while maintaining environmental sustainability. To address these challenges, future crops should have characteristics suitable for sustainable agriculture development: maximal net production and minimal effects on ecology. The Breeding 4.0 era is marked by the ability to rapidly, rationally and precisely combine any known beneficial alleles into desirable combinations (Wallace *et al.*, 2018). To reach the goals of Breeding 4.0, we need to develop a roadmap for future crop design. In particular, we have to identify specific beneficial alleles that are responsible for desirable variations in crops, purge deleterious variants and apply new cutting-

edge technologies, such as advanced genome sequencing pipelines, big data deep learning, high-throughput phenotyping platforms, precise genome-editing tools and synthetic biology methods.

STRATEGIES TO DESIGN FUTURE CROPS

Improvement of current well-cultivated crops

The first straightforward strategy for designing future crops that meet sustainable agriculture requirements is to improve the following aspects of current well-cultivated crops.

Increasing yield. It is estimated that the yields of major crops need to increase at a rate of 2.4% per year to meet the food supply demand by 2050. However, the current growth rates of the four major crops, maize (*Zea mays*), rice (*Oryza sativa*), wheat (*Triticum aestivum*), and soybeans (*Glycine max*), are only approximately half of this anticipated rate (Ray *et al.*, 2013). The development of new varieties with high yield potential that can fill this gap is the foremost mission of the Future Crops Design project. In fact, in a trial, it was reported that a super-high-yield rice variety could produce one- to threefold more grains under optimal conditions than in normal paddy fields (Liu *et al.*, 2020a).

Improving nutritional quality. Although the amount of food supply has been significantly improved in the last half-century, changes in human lifestyle and food consumption have resulted in a phenomenon called hidden hunger (Nair *et al.*, 2016). For instance, in sub-Saharan Africa and America, about 17–30% of children under the age of 5 years have an inadequate daily intake of Vitamin

A (Harjes *et al.*, 2008; Haskell, 2012). It has been reported that about two billion people are suffering from a chronic deficiency of micronutrients (WHO, 2008), a new threat to human health. Moreover, the incidence of type-2 diabetes, obesity and colon disease has markedly increased in the past decade (Zhou *et al.*, 2016). Hence, the second mission of the Future Crops Design project is to generate crops with higher/balanced nutritional quality or specialized metabolites using metabolic engineering and synthetic biology approaches (Francis *et al.*, 2017; Martin and Li, 2017; Sweetlove *et al.*, 2017; Vasconcelos *et al.*, 2017).

Increasing agricultural resource use efficiency. It was reported that ~17% of arable land has lost productivity since 1945 due to inappropriate agriculture management (Oldeman, 1994). In fact, nutrient-use efficiencies of today's crops only reach 30–50% for nitrogen fertilizer (Cassman *et al.*, 2002) and ~45% for phosphorus fertilizer (Smil, 2000). Moreover, fresh water has become a limiting factor for agriculture in many areas in the world. It is estimated that about 2800 km³ of fresh water per year is used for agricultural irrigation, and that crop production decreases by ~20% without irrigation (Siebert and Doll, 2010). Therefore, to reduce agricultural inputs and environmental burdens, we should aim to develop high nutrient- and water-use efficiency crops without yield penalty.

Improving biotic and abiotic stress tolerance. To further achieve sustainable agriculture, a reduction in the use of pesticides is extremely important. The introduction of crops with improved tolerances to pathogens and viruses can significantly reduce environmental pollution, and at the same time minimize crop yield loss (Nelson *et al.*, 2018). As the occurrence of extreme weather events has dramatically increased in the past decade (Zhang *et al.*, 2019), there is an urgent need to improve the resistance of major crops to abiotic stresses as well (Varshney *et al.*, 2018). The custom design of crops with strong tolerance to a specific type of abiotic stress can benefit agriculture in marginal lands, where the soil is vulnerable to degradation and unable to sustain the growth of high-yield crops (Tilman *et al.*, 2002).

De novo domestication

Domestication of major crops began ~12 000 years ago. It has been estimated that over 2500 plant species, spanning 160 taxonomic families (Meyer and Purugganan, 2013), have been domesticated or semi-domesticated for food. However, only 150 of them have been commercially cultivated to some degree, with merely 20 plant species comprising 90% of the world's calories (McKell, 1983). At present, three major crops—rice, wheat and maize—provide 60% of the calories consumed by humans (Khoury *et al.*, 2014; Massawe *et al.*, 2016).

Domestication is a human-guided process that encompasses four stages: the onset of domestication; the fixation of desirable alleles; the generation of cultivated populations; and finally, selective breeding (Purugganan and Fuller, 2009; Meyer and Purugganan, 2013). Along with the promotion of Green Revolution technologies, increasing homogeneity in the global food supply occurs (Khoury *et al.*, 2014). From a genetic diversity perspective, this homogeneity has become a potential threat to modern agriculture because it causes an increase in disease incidence and the risk that plants will be unable to cope with unanticipated environmental changes in the future. Therefore, besides improvement of current well-cultivated crops, the second avenue for future crop design is *de novo* domestication of wild or semi-wild plants through genetic modification of the homologous domestication genes.

Domestication of neglected or orphan plants. During the development of agriculture, some wild plants, for example millet, were semi-domesticated, but were finally abandoned due to the rapid development of other major crops (Meyer and Purugganan, 2013; Fernie and Yan, 2019). Certainly, there are more wild plants that are relatively unknown to the public and have not experienced intensive artificial selection. These plants are often termed 'orphan' plants. Although neglected semi-domesticated and orphan plants usually have low productivity and cannot be grown at a large agricultural scale, they do harbor excellent properties for particular traits, such as high nutritious value, high stress tolerance or enrichment of specialized metabolites. Therefore, naturally stress-resilient orphan plants have been proposed as an important source of germplasm for the generation of high-production stress-tolerant crops (Zhang *et al.*, 2018).

Many crop species have similar domestication traits. Domestication syndrome refers to a suite of phenotypic traits arising during domestication that distinguish crops from their wild progenitors (Doebley *et al.*, 2006; Fernie and Yan, 2019). Interestingly, growing evidence suggests that both common and convergent mechanisms underlie the domestication syndrome (Lenser and Theissen, 2013). For example, the glutinous grain improvement traits in rice, sorghum, barley and millet are all controlled by orthologs of the *Waxy* gene (Meyer and Purugganan, 2013), whereas the stay-green gene *G* controls seed dormancy in a range of species including soybean, rice and *Arabidopsis* (Wang *et al.*, 2018b). On the basis of these conceptual advances, considerable attention has been recently directed on the *de novo* domestication of wild plants or semi-wild plants into new complementary crops (DeHaan *et al.*, 2016; Massawe *et al.*, 2016; Osterberg *et al.*, 2017; Eshed and Lippman, 2019). Quinoa (*Chenopodium quinoa*), one of the healthiest and most nutritious foods, stands as a good example. Quinoa seeds are gluten-free with a low

glycemic index, and contain an excellent balance of essential amino acids, fiber, lipids, carbohydrates, vitamins and minerals (Jarvis *et al.*, 2017). With the release of the quinoa genome and establishment of a tissue culture system (Jarvis *et al.*, 2017; Zou *et al.*, 2017), further domestication of present quinoa cultivars will be not only an important means for tackling world food security, but also a new avenue for providing healthy food (Jarvis *et al.*, 2017).

The requirement for high-quality natural rubber has increased in the past two decades. However, increasing natural rubber production from the rubber tree (*Hevea brasiliensis* L.), currently the only major commercial source for natural rubber, is not possible because of its limited planting area, narrow genetic background, susceptibility to severe diseases and large labor requirements. To meet the demand for natural rubber, the rubber dandelion (*Taraxacum kok-saghyz*), which produces the same or even better quality natural rubber (van Beilen and Poirier, 2007; Cherrian *et al.*, 2019), has recently been selected as a candidate for *de novo* domestication (Lin *et al.*, 2018).

Domestication of perennial crops. Although most plants in the wild are perennials, cereal, legume and oilseed crops, which are staples of the global food supply, are annuals (Glover *et al.*, 2010). Because annual crops have less extensive, shorter-lived root systems and need to be sown every year, they usually exhibit a lower capacity for nutrient and water uptake, and a tendency to disturb the soil and pollute the water system through nitrate and herbicide leaching (Cox *et al.*, 2010). In contrast, perennial crops do not need to be sown every year, tend to have longer growing seasons and long-lived deep root systems, maintain and utilize nutrients and water efficiently, and have wide stress tolerance (DeHaan *et al.*, 2005; Cox *et al.*, 2006; Culman *et al.*, 2013; Kantar *et al.*, 2016). In addition, perennial crops can store more carbon in soil than annual crops (Robertson *et al.*, 2000). Therefore, generation of diverse and perennial grain-cropping systems is increasingly proposed as an important means for sustainable agriculture development (Glover *et al.*, 2007). For example, perennial wheat, maize and sorghum are being developed by performing outcrosses between annual cultivars and related wild species. The development of perennial crops requires improvement of the major determinants of agronomic traits, including plant architecture, flowering time, seed number and size, dormancy, food quality and nutrient use efficiency (Kantar *et al.*, 2016). Although the yields of undomesticated or semi-domesticated perennial plants are still low, it is predicted that yield can be greatly improved by artificial selection and proper agricultural environment management (DeHaan *et al.*, 2005).

Redomestication of current cultivated crops. Domestication is the process of artificially selecting traits to meet

human requirements. In general, domesticated crops exhibit superior and distinct traits compared with their progenitors. For instance, cultivated soybean seeds have higher oil and lower protein contents than wild soybean seeds (Zhou *et al.*, 2015). Domestication has always been a dynamic process. To meet new requirements of humans, existing crops or their ancestors can be directed toward another evolutionary route by exposure to new artificial selection pressures, a process known as redomestication (Meyer *et al.*, 2012; Sang and Ge, 2013). It has been proposed that redomestication of current high-oil-content cultivated soybean into a new high-protein-content crop can be a promising approach to tackling the problem of livestock feed shortages (Patil *et al.*, 2017). Similarly, an effort has been made to enable maize to regain its ability to produce oil-containing oleic acids (Zheng *et al.*, 2008).

FAPPROACHES

Although the generation of future crops that meet the demand for food and ecology security is a big challenge, rapid advances in biotechnology are making it possible.

Genomics and comparative genomics

The release of the first plant genome in 2000, that is, the Arabidopsis genome, was a turning point for plant genomics (Theologis *et al.*, 2000). Thereafter, with the development and application of next-generation sequencing (NGS) technologies, a vast number of reference genomes for crops including rice, maize and wheat were assembled (International Rice Genome Sequencing Project, 2005; Schnable *et al.*, 2009; Schmutz *et al.*, 2010; Shendure *et al.*, 2017; International Wheat Genome Sequencing *et al.*, 2018; Shen *et al.*, 2018, 2019). In addition to assisting *de novo* assembly of plant genomes, the high amount of data generated by NGS, also known as genome resequencing, has reshaped the strategies used for population genetic studies, which in turn have accelerated our understanding of gene evolution at the population level (Lister *et al.*, 2009; Huang and Han, 2014; Koenig and Weigel, 2015; Weigel and Nordborg, 2015).

Nevertheless, to accomplish the goals of future crop design, particularly the domestication of orphan crops, more high-quality reference genomes are needed. The recently launched Earth BioGenome Project (EBP; Lewin *et al.*, 2018; Exposito-Alonso *et al.*, 2020), which aims to produce reference genomes for all eukaryotic species within the next decade, is timely and can offer us unprecedented opportunities.

Understanding the principles underlying domestication is the key to future crop design (Ross-Ibarra *et al.*, 2007; Morrell *et al.*, 2011; Olsen and Wendel, 2013). With more genomes from different species becoming available, phylogenomics analyses can be performed to address a number of basic and important evolutionary questions, such as

how an agronomic trait is selected during domestication, how the changes in coding and non-coding sequences contribute to trait formation, and why resistant genes are often lost during domestication. Certainly, this knowledge will be valuable for the rational design of crops. For instance, through a genome-wide comparative analysis of 37 plant species, Griesmann *et al.* revealed that multiple independent gene loss events occurred during the evolution of non-nitrogen-fixing plants (Griesmann *et al.*, 2018). The analyses of these mutated genes and their underlying regulatory mechanisms will lay the groundwork for the generation of the long-sought-after nitrogen-fixing non-legume crops (Stokstad, 2016).

Although a single reference genome for a plant family is largely sufficient to identify single nucleotide polymorphisms (SNPs) or small indels within a population, there has been an increasing awareness that one or a few reference genomes is far from sufficient for fully covering the genetic diversity of a species because of the existence of a considerable number of structural variations among individuals (Saxena *et al.*, 2014). Therefore, pan genome analyses of major crops has become prevalent and the new standard for crop genomics in recent years (Golicz *et al.*, 2016; Tao *et al.*, 2019; Bayer *et al.*, 2020). Moreover, graph-based pan genome analyses of crops have just started to be applied; in these analyses all the genetic diversity of a species is integrated into one genome instead of multiple individual genomes from a single lineage, enabling fast and accurate genotyping (Garrison *et al.*, 2018; Aneur, 2019; Rakocevic *et al.*, 2019; Liu *et al.*, 2020b).

Dissection of molecular mechanisms controlling agronomic traits

To further increase crop production, rational design of future crops with ideal architecture, high resistance toward diseases and pests, increased water and nutrient use efficiencies, and improved quality in terms of metabolites is needed. Undoubtedly, the accomplishment of this ambitious goal will be based on our growing knowledge of the molecular mechanisms underlying these agronomic traits. Here, we use the study of the genetic basis of shoot architecture as an example to explain why continuous support of plant basic research is important for future crop design.

Shoot architecture is fundamentally important to growth and productivity in crops. Selection of plants with certain architectural features and phenological characters that result in higher yield of seeds and fruits is one of the key innovations of crop domestication over the last 10 000 years. For instance, one of the most important domestication steps in maize was transition from a highly branched grass, namely teosinte (*Z. mays* ssp. *parviglumis*), from Central America, to a plant comprising a single stem with a single terminal male inflorescence (tassel) and a lateral female inflorescence (ear). Interestingly, genetic

studies have revealed that a mutation in a single gene, which encodes a Teosinte-branched1/Cycloidea/Pro-liferating (TCP) transcription factor encoding gene *TEOSINTE BRANCHED1* (*TB1*), is sufficient to trigger these fundamental changes in shoot architecture (Doebley *et al.*, 1997; Wang *et al.*, 1999; Studer *et al.*, 2011). Another well-known example is the introduction of a semi-dwarf architecture during the domestication of wheat and rice, also known as 'Green Revolution' (Khush, 2001). Although selected independently, the casual mutations leading to the semi-dwarf architecture in wheat and rice are surprisingly similar. It has been shown that the deactivation of metabolism or signaling of the plant hormone gibberellic acid is the major driver of the semi-dwarf architecture (Peng *et al.*, 1999; Monna *et al.*, 2002).

During the past 20 years, tremendous efforts have been made to understand the molecular basis of plant architecture. The regulatory mechanisms underlying stem elongation, thickness and stem/leaf angle have been revealed (Luo *et al.*, 2016; Mantilla-Perez and Salas Fernandez, 2017; Singh *et al.*, 2017). For instance, *PROSTRATE GROWTH1*, encoding a nuclear-localized C₂-H₂ zinc-finger protein, has been identified as a master gene regulating the transition from the prostrate to erect growth habit during rice domestication (Jin *et al.*, 2008; Tan *et al.*, 2008). Mapping and identification of genes that regulate rice architecture including stem height and thickness led to the discovery of *IDEAL PLANT ARCHITECTURE1* (*IPA1*; Jiao *et al.*, 2010).

With the maturation of forward and reverse genetics approaches during the past two decades, a large number of mutants showing altered shoot branch number have been identified and characterized at both the phenotypic and molecular levels (Wang *et al.*, 2018a). Genetic interactions of these regulatory genes that control shoot branching in Arabidopsis have revealed *BRC1*, an ortholog of *TB1* in maize, as a signal integrator that represses axillary bud outgrowth (Wang *et al.*, 2019). Importantly, physiological and mutant analyses have further demonstrated the critical roles of nutrition (sugar) and phytohormones (auxin, cytokinin and strigolactones) in the initiation of and outgrowth of lateral shoots (Wang and Jiao, 2018; Barbier *et al.*, 2019; Hill and Hollender, 2019).

Inflorescence architecture also exerts great impact on the number of seeds and fruits and final yield in crops. Sophisticated developmental biology studies have revealed that inflorescence architecture is regulated by flowering time and floral meristem determination genes (Teo *et al.*, 2014; Wang *et al.*, 2018a). For example, the flowering time gene *TERMINAL FLOWER1* in Arabidopsis and its orthologs *RICE CENTRORADIALIS* in rice and *SELF-PRUNING* in tomato play important roles in inflorescence architecture by maintaining shoot identity (Liu *et al.*, 2013). Similarly, the evolutionarily conserved Arabidopsis *LSH1*

and *Oryza G1 (ALOG)* family genes modulate inflorescence architecture partly through regulation of floral meristem identity genes in both rice and tomato (MacAlister *et al.*, 2012; Yoshida *et al.*, 2013).

The 'ideal plant architecture' for rice has been proposed to be few unproductive tillers, a large number of grains per panicle and thick stems (Donald, 1968; Khush, 1995; Wang *et al.*, 2018a). The identification of the abovementioned key regulators of plant architecture now offers us an unprecedented opportunity to rationally design future crops with the ideal architecture. In general, this goal can be achieved by precise marker-assisted breeding, pyramiding major genes that significantly contribute to grain quality and yield (Qian *et al.*, 2016; Zeng *et al.*, 2017), or direct genome editing of the genes associated with domestication (Khan *et al.*, 2019; Figure 3). For example, the rare alleles of *IPA1*, namely *ipa1-1D* and *ipa1-2D*, have been proven to significantly increase grain yield by reducing tiller number (Jiao *et al.*, 2010; Zhang *et al.*, 2017). Similarly, it has been recently demonstrated that introgression of the wild *Upright Plant Architecture2* allele into modern hybrids and editing a B3-domain transcription factor (*ZmRAVL1*) enhance maize grain yield under high planting densities (Tian *et al.*, 2019). In *Solanaceae*, the power of clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein-9 nuclease (Cas9) (CRISPR-Cas9) tools in rapid improvement of domestication traits in an orphan *Solanaceae* crop and *de novo* domestication of wild tomato species has been demonstrated (Rodriguez-Leal *et al.*, 2017; Lemmon *et al.*, 2018; Li *et al.*, 2018; Zsogon *et al.*, 2018). Importantly, CRISPR-Cas9-based genome editing of promoters generates diverse cis-regulatory alleles that provide beneficial quantitative variation for breeding (Rodriguez-Leal *et al.*, 2017).

In conclusion, identification of domestication genes by forward genetics, discovery of rare alleles of key regulators controlling agronomic traits through pan-genome analyses, and identification of transcription factors and associated gene regulatory cis-elements by developmental genetics provide us valuable molecular substrates for crop design in the future.

New technologies

Rational design of future crops can also benefit from the recent development of new integrative omics tools, advanced genome-editing tools and synthetic biology approaches.

Next-generation plant genomics and phenomics. Detailed knowledge of a genome, specifically a genotype-to-phenotype map, is essential for targeting and rapidly prototyping the optimal candidates for future crop design. With the development of long-read sequencing technologies and genome assembly pipelines, the cost of sequencing a plant

has remarkably decreased. Pan-genome analyses of major crops including rice, soybean and maize have recently been reported (Hirsch *et al.*, 2014; Jin *et al.*, 2016; Zhao *et al.*, 2018; Liu *et al.*, 2020b). These data-rich resources have laid the groundwork for identification of genes associated with agronomic traits by quantitative trait locus mapping or genome-wide association study (GWAS). Importantly, a single mapping population can be simultaneously used for identifying genes responsible for distinct agronomic traits.

Conventional GWAS designs and methods have their own limitations (Nordborg and Weigel, 2008). For example, GWAS has low power to map multiple functional alleles within one gene and to identify rare alleles within a population. Moreover, highly differentiated population structure is emerging as the biggest problem for GWAS of rice, which is a selfing species (Zhou and Huang, 2019). To overcome these difficulties, use of a combination of permanent populations such as nested association mapping (NAM) populations and multi-parent advanced generation intercross (MAGIC) populations, high-profile omics data, and next-generation analysis approaches based on machine learning algorithms has been proposed (Zhou and Huang, 2019). It should also be noted that, due to over-representation of structural variants in plant genomes, conventional SNP-based GWAS cannot be applied to all crops, especially those polyploid plants that do not have a high-quality reference genome. Fortunately, in light of studies in bacteria, a *k*-mer-based GWAS method has been recently developed (Voichkek and Weigel, 2020). This new approach may pave the way for GWAS analyses in plants without a complete or high-quality genome sequence.

With the above efforts to identify agronomic trait genes using advanced genomics tools, profiling crop phenotypes associated with allelic variants and environments remains a major technical bottleneck (Yang *et al.*, 2013; Tardieu *et al.*, 2017). Plant phenomics not only assigns a genotype to one phenotype under a given growth condition, but also characterizes the phenotypic plasticity of plants when exposed to diverse environmental conditions. Because the yield of a given genotype often differs among field sites, it is particularly important to establish an automatic, long-term phenomics platform for crops with a long life cycle under a wide range of growth conditions.

Precisely associating multiple phenotypes to a genotype requires acquisition and analyses of distinct architectural variables at both spatial and temporal scales, and compatible with distinct environmental conditions (growth chamber or field). Unfortunately, no single plant phenomics platform can currently analyze every scale or environment. An example of phenotyping at a high-resolution level (from single cell to organ level) is X-ray micro-computed tomography, which has been developed to uncover adaptive mechanisms of lateral root branching in response to environmental signals (Bao *et al.*, 2014). The

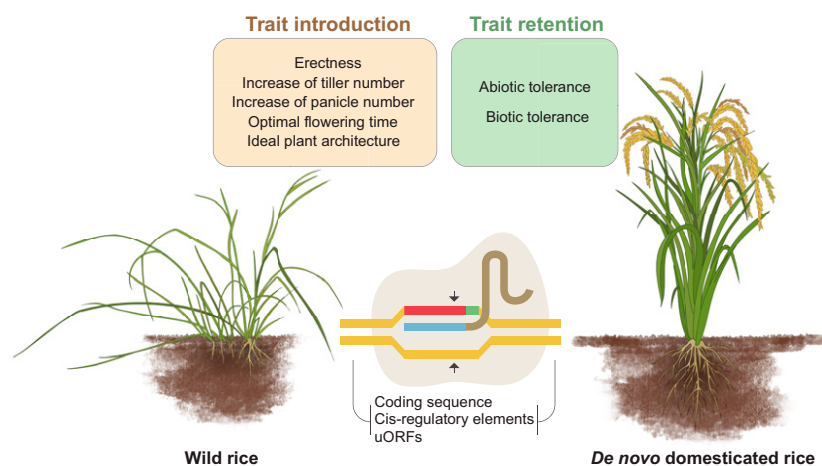


Figure 3. Direct genome editing of the genes associated with domestication. Genome-editing tools enable rapid *de novo* domestication of wild plants, while, at the same time, retain the genes responsible for abiotic and biotic tolerance.

implementation of time-lapse imaging, ionomics tools (such as ICP-MS), computer modeling and genotyping datasets has led to the identification of new physiological mechanisms that allow plants to respond to changes in environmental conditions, and to the elucidation of the underlying genetic circuits (Tardieu *et al.*, 2017). At the macro (low-resolution) level (from a plant to canopy), highly automated platforms enable researchers to perform 4D whole-plant imaging and characterize shoot/root architecture of plants grown under greenhouse conditions. Multi-spectral 4D analyses with ground-based platforms and aerial platforms further offer the possibility of investigating the genetic basis of flowering time and yield of diverse crops in a variety of environmental scenarios (Furbank *et al.*, 2019).

With the development of novel sensors and imaging techniques, methodological advances in data acquisition, processing and standardization (i.e. digitation and quantification of variables) are becoming increasingly important (Perez-Sanz *et al.*, 2017). First, the proper identification and high-quality imaging of objects (e.g. shoot, leaf or flower), especially under field conditions, is required for data pre-processing. New technologies such as high-definition LIDAR (light detection and ranging) or multi-hyperspectral cameras have shown great potential to meet this demand. Second, artificial intelligence (AI)-based data analysis and different algorithms are being applied to data processing to avoid distortions and improve throughput and reproducibility (Bolger *et al.*, 2019). Third, to make data reusable and interoperable for the whole community, use of MIAPPE (Minimal Information about Plant Phenotyping Experiments) is recommended to ensure proper description of all necessary metadata for every experiment (Krajewski *et al.*, 2015; Cwiek-Kupczynska *et al.*, 2016).

Taken together, we are witnessing the next revolution in functional genomics, where the gap between genotype and phenotype can be bridged using a combination of approaches, such as NGS, robotics systems, AI and

classical plant physiology. The explosion of genomics data and innovation in phenotyping technologies will definitely modernize plant biology, and accelerate the progress in both fundamental plant science and applied breeding research in the future.

Advanced genome-editing tools. The recent development and application of technologies based on CRISPR-Cas9 have made the targeted and precise genetic manipulation of crops a reality (Altpeter *et al.*, 2016; Ran *et al.*, 2017; Chen *et al.*, 2019; Hua *et al.*, 2019; Zhang *et al.*, 2020). The improvement of crop yields, quality and stress resistance can be achieved by knockout and/or activation of one or several genes that confer undesirable traits. Because many agriculturally important traits are conferred by SNPs in the non-coding intergenic regions or by dominant gain-of-function point mutations in the protein coding sequence, CRISPR-mediated base editors are now becoming a commonly used tool for crop engineering (Li *et al.*, 2020). Meanwhile, the development of targeted insertion methods using prime editing or chemically modified donor DNA, and fine-tuning gene expression by the dCas9-derived synthetic transcription modulator (e.g. dCas9-Sun-Tag and dCas9-TV system) have greatly expanded the scope and capabilities of genome editing in crops (Lowder *et al.*, 2015; Piatek *et al.*, 2015; Vazquez-Vilar *et al.*, 2016; Li *et al.*, 2017; Anzalone *et al.*, 2019; Papikian *et al.*, 2019; Lin *et al.*, 2020; Lu *et al.*, 2020).

The chloroplast (plastid) constitutes a hotspot for cellular metabolic activities, including photosynthesis and biosynthesis of secondary metabolites. Therefore, another important future direction is the development of feasible tools for organelle genome editing in crops. However, the application of transplastomic technology to major crops has proven extremely challenging, and the species range of plastid transformation is still very limited (Maliga and Bock, 2011; Bock, 2015; Fuentes *et al.*, 2018). Editing of the chloroplast genome by CRISPR-Cas9 has so far not been

achieved. Very recently, using an interbacterial cytidine deaminase toxin specific for double-stranded DNA, a CRISPR-free, RNA-free base editor that can introduce targeted mutations in the human mitochondrial genome has been developed (Mok *et al.*, 2020). The application of this method may thus open up a new door for chloroplast genome editing in the future.

Plant transformation and gene delivery. One of the bottlenecks for future plant biotechnology is the lack of a universal plant transformation protocol (Atkins and Voytas, 2020). Because they were developed in the 1950s, *de novo* shoot regeneration and somatic embryogenesis have been widely used for the generation of genome-modified (GM) crops. However, only a limited number of major crop cultivars can be transformed at high efficiency. Although introduction of a combination of totipotent genes, such as maize *WUSCHEL2* and *BABY BOOM*, greatly increases transformation rate (Lowe *et al.*, 2016), its application is largely restricted to a few cereals. To date, the regeneration rate for cotton and soybean is still far from satisfactory. Therefore, the development of a suitable protocol for most crop cultivars, especially for some wild species, is an important research direction.

One promising research direction is to create transgenic plants without tissue culture; one such method has been developed recently for the *de novo* induction of gene-edited meristems by co-delivery of totipotent genes and gene-editing reagents into the somatic cells of dicotyledonous crops such as tobacco, tomato, potato and grape (Maher *et al.*, 2020). Moreover, highly efficient gene-editing methods based on plant viruses have been achieved in *Solanaceae* (Ellison *et al.*, 2020; Ma *et al.*, 2020). However, whether these protocols can be adopted in cereals remains to be addressed.

Another possible approach for generation of transgenic crops without tissue culture is based on nanotechnology. For example, a novel transformation platform technology, namely pollen magnetofection, has been used to generate transgenic cotton plants without regeneration (Zhao *et al.*, 2017). Moreover, the rapid improvement of DNA delivery carriers, such as high-aspect ratio nanomaterials, has enabled delivery of functional genetic materials with high efficiency (Demirer *et al.*, 2019, 2020).

Despite these advances in gene delivery and nanotechnologies, understanding the molecular basis for *de novo* shoot regeneration and somatic embryogenesis is still a fundamental question in the field. The identification of plant transcription factors with features similar to those of Yamanaka factors in animals will surely accelerate the development of new plant transformation routes in the future (Takahashi and Yamanaka, 2006).

Synthetic biology approaches. Synthetic biology is an emerging field that combines engineering principles with

biology toward the design and production of novel biological parts, devices or systems. This field is developing rapidly, and may play an important role in future agricultural crop improvement (Liu and Stewart, 2015; Nemhauser and Torii, 2016; Kubis and Bar-Even, 2019; Leydon *et al.*, 2020). Phytoremediation was among the earliest examples of successful metabolic engineering in plants. For instance, overexpressing a secretory laccase in transgenic *Arabidopsis* plants allows *ex planta* phytoremediation of trichlorophenol and phenolic allelochemicals (Wang *et al.*, 2004).

Currently, targeted plant metabolic engineering can be achieved at different levels (Erb *et al.*, 2017). At a basic level, the productivity of a metabolic pathway can be reinforced through gene deletion or overexpression. The metabolic solution space can be further expanded by the introduction of a combination of existing enzymes. The resulting reconstituted metabolic network enables redirection of metabolic flux toward a desired product. For example, it was reported that engineering more efficient photorespiratory pathways into tobacco while inhibiting the native pathway markedly increases both photosynthetic efficiency and vegetative biomass (South *et al.*, 2019).

At a more advanced level, introduction of new reactions that are not known to exist in nature through enzyme engineering or *de novo* enzyme design can go beyond existing metabolic network structures and create a true 'synthetic metabolism' pathway. For instance, a synthetic CO₂-fixation pathway, named the CETCH cycle, with 17 different enzymes from nine different organisms was developed recently (Schwander *et al.*, 2016). Undoubtedly, development and application of metabolic engineering tools will pave the way for design of future crops with balanced nutrition and a superior CO₂ conversion rate.

Engineering plant receptors has proved to be another powerful approach to rewire endogenous signal transduction pathways. In the early 2000s, a pioneer project that created a chimeric leucine-rich repeat receptor kinase to evoke disease resistance upon the exogenous application of a plant hormone was reported (He *et al.*, 2000). Structure-guided receptor engineering has now become one of the new fronts of plant synthetic biology. An excellent example comes from engineering of the abscisic acid (ABA) receptor, which plays a critical role in allowing plants to cope with drought stress. Through directed mutagenesis, Park *et al.* (2015) successfully generated a receptor variant that perceives a fungicide, mandipropamid, and triggers an ABA response, thereby boosting drought tolerance.

Spatial and temporal modulation of gene expression could also serve as a synthetic approach for crop design in plants. For example, expression of a chloroplast gene, *D1*, which encodes a protein involved in the repair of

photosystem II, in the nuclear genome, significantly increases biomass and grain yield at higher temperatures (Chen *et al.*, 2020).

To sum up, plant synthetic biology will play an increasingly important role in meeting the increasing demand for food, biofuels and metabolites. The application of synthetic biology principles and methodologies in the microbial field has enabled researchers to design future elite crops with human and environmental benefits. Undoubtedly, improvements in the transformation efficiency of crops and genome-editing tools will accelerate plant synthetic biology design cycles.

PERSPECTIVES AND CHALLENGES

In general, a single agronomic trait is controlled by multiple quantitative loci, and different agronomic traits are to some extent correlated and are frequently regulated in modularity. This complexity creates a major barrier for conventional breeding (Klingenberg *et al.*, 2001; Chen and Lubberstedt, 2010), and one of the biggest challenges for future crop design is to break undesired tradeoffs among different traits, especially those related to crop yield and abiotic or biotic stress resistance. For instance, as discussed above, although they are high yielding, the semi-dwarf Green Revolution varieties often require an increased supply of high-nitrogen fertilizer and water. Therefore, to further improve current crops, there is a need to increase the fertilizer- and water-use efficiencies, and to enhance stress tolerance without yield penalty. The rational design of future crops with these characteristics is the key scheme of Breeding 4.0 (Wollenweber *et al.*, 2005; Pingali, 2012). To achieve this goal, genome-wide dissection of the regulatory networks underlying the hub genes that are responsible for agronomical trait formation is extremely important (Kumar *et al.*, 2015; Jansson *et al.*, 2018). This will definitely require continuous support from funding agencies and global collaborations.

With the rapid development of genome-editing tools in the past decade, the generation of GM crops has again raised human health and environmental safety considerations (Friedrichs *et al.*, 2019). Although there is broad scientific consensus that GM crops pose no greater risk to consumers than conventional agricultural products, the promotion of GM crops is heavily restricted in many countries, including European nations and China. Because of the precision of genetic changes introduced by CRISPR-Cas9 tools, it is suggested that genome-edited crops (GECs) should be subjected to product-based rather than technology-based regulation. In particular, GECs with gene knockouts or nucleotide variants that have been documented to exist in cultivars or closely related wild species have to be carefully evaluated. In 2016, a regulatory framework for GECs was proposed (Huang *et al.*, 2016). These regulations include minimization of the risk of the escape

of GECs from laboratories and fields at the early stages of research and development, avoidance of the introduction of foreign DNA sequences and off-target DNA editing events, and precise documentation of DNA sequence changes at the target sites by whole-genome sequencing. It is definitely necessary for scientists, policy-makers, regulators and journalists to coordinate and discuss how to improve global food security using genome-editing tools, and at the same time alleviate public concerns related to GECs (Callaway, 2018).

ACKNOWLEDGEMENTS

The authors apologize to those whose work we were unable to cite owing to space constraints. The authors thank Xuehui Huang for valuable comments on the manuscript. This work was supported by the grants from National Natural Science Foundation of China (grant number 31788103) and Strategic Priority Research Program of the Chinese Academy of Sciences (grant number XDA24000000).

AUTHOR CONTRIBUTIONS

ZT, J-WW, HB and JL wrote the manuscript.

CONFLICT OF INTEREST

The authors declare no competing financial interests. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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