

Developing naturally stress-resistant crops for a sustainable agriculture

Heng Zhang^{1,2*}, Yuanyuan Li³ and Jian-Kang Zhu^{1,4*}

A major problem facing humanity is that our numbers are growing but the availability of land and fresh water for agriculture is not. This problem is being exacerbated by climate change-induced increases in drought, and other abiotic stresses. Stress-resistant crops are needed to ensure yield stability under stress conditions and to minimize the environmental impacts of crop production. Evolution has created thousands of species of naturally stress-resistant plants (NSRPs), some of which have already been subjected to human domestication and are considered minor crops. Broader cultivation of these minor crops will diversify plant agriculture and the human diet, and will therefore help improve global food security and human health. More research should be directed toward understanding and utilizing NSRPs. Technologies are now available that will enable researchers to rapidly improve the genetics of NSRPs, with the goal of increasing NSRP productivity while retaining NSRP stress resistance and nutritional value.

A sustainable agriculture needs to address the challenges of food security and human health while leaving as small environmental footprints as possible¹. By the year 2050, the current level of food production must increase by at least 70% to meet the demands of a growing world population and shifting dietary preferences towards more animal products, while 38% of the world's land and 70% freshwater are already used for agriculture². Abiotic stresses, including drought, high and low temperatures, soil salinity, nutrient deficiencies and toxic metals, are the leading cause of yield loss, decreasing crop productivity by 50–80% depending on the crop and geographical location³. Thus, developing stress-resistant crops that can have stable yields under stress conditions is an important strategy to ensure future food security². This need is particularly urgent considering the increased frequency of extreme weathers that accompany the global climate change, which cause more severe environmental stresses, more frequent plant disease outbreaks and reduced grain quality^{4–6}.

Crop production can be increased through agricultural expansion into uncultivated terrestrial areas and/or agricultural intensification that increases the yield per unit of cropland. The latter, exemplified by the Green Revolution (GR), is the dominant force-driving crop production gains during the past half century and helps preserve natural ecosystems by reducing the need for expansion of agriculture into virgin land⁷. Agricultural intensification has been especially important for cereals. From 1964 to 2014, world cereal production almost tripled with only an 8% increase in land use⁸. However, the trend of yield increase in these and other major crops is worrisome. A recent study indicates that the yield of four major crops (maize, rice, wheat and soybean) stopped rising in 24–39% of the world's growing area⁹. The rate of increase in grain yields declined from 1961 to 2007 (ref. ¹⁰) and a higher sensitivity to drought was found correlated with yield increases in crops like maize and soybean¹¹. This is partly because that the modern varieties of these major crops have a narrow genetic base, and it has become increasingly difficult to improve genetic gains in current high-yielding cultivars¹².

The success of agricultural intensification also comes with a huge ecological cost. The innovation of the GR includes the development of genetically improved high-yield modern varieties and a series of agronomic practices including irrigation, increased use of fertilizers and pesticides, and mechanization⁷. Agricultural intensification has been limited to a small number of major crops (rice, wheat, corn, soybean and potato), which now provide much of the calorie intake for humans. Large areas of monoculture raise the risk of disease outbreaks¹³. Massive application of fertilizers and pesticides disrupts global nitrogen and phosphorus cycles, reduces biodiversity, and causes aquatic pollution¹. Thus crops that utilize water and fertilizers more efficiently and require less pesticides are urgently needed for agriculture to be sustainable.

In the past, most breeding efforts aimed for high crop yields. As a result, few of the modern varieties are stress resistant¹⁴. Beneficial alleles that contribute to stress resistance or grain nutrition are often lost during conventional breeding because they do not contribute directly to yield of the major crops (for an example, see ref. ¹⁵). Modern breeding programs aiming at increasing stress resistance go back to traditional landraces¹⁶ and/or wild relatives of the major crops for favourable stress resistance alleles¹². An often mentioned example is the improvement of salt resistance in the tetraploid durum wheat, which is more sensitive to salt compared to the bread wheat. By crossing a modern durum wheat variety named *Tamaroi* to a diploid wild relative, *Triticum monococcum*, a plasma membrane Na⁺ transporter gene from *T. monococcum* (named *TmHKT1;5-A*) was incorporated into *Tamaroi*, increasing yield by 25% in soil with an average salt concentration of 169 mM¹⁷. Similar examples that improve stress resistance with single gene alleles are rare. The difficulty in breeding stress-resistant cultivars has been attributed to the complex genetic architecture of stress responses (that is, controlled by many small-effect quantitative trait loci and their complex interactions) and to the variations in the duration, severity and combinations of stresses that plants may encounter in the field^{18,19}. To solve this problem, researchers have proposed that

¹Shanghai Center for Plant Stress Biology, Center for Excellence in Molecular Plant Sciences, Chinese Academy of Sciences, Shanghai, China. ²National Key Laboratory of Plant Molecular Genetics, Center for Excellence in Molecular Plant Sciences, Chinese Academy of Sciences, Shanghai, China. ³Key Laboratory of Plant Stress Research, Shandong Normal University, Jinan, Shandong, China. ⁴Department of Horticulture and Landscape Architecture, Purdue University, West Lafayette, IN, USA. *e-mail: zhangheng@sibs.ac.cn; jkzhu@sibs.ac.cn

mathematical modelling be used to assess the interactions among multiple quantitative trait loci (QTLs) and various environmental conditions²⁰, or that a combination of modelling and field experiments be used to identify the heritable and non-heritable sub-traits associated with stress resistance²¹.

During the past two decades, considerable progress has been made in understanding the responses of plants to abiotic stresses and their signal networks in both the model plant *Arabidopsis thaliana*²² and several major crops²³. Hundreds of genes and QTLs involved in plant stress responses have been identified. Although manipulating the function of many of these genes can increase stress resistance under controlled laboratory conditions, such manipulations have rarely produced a stress-resistant cultivar that performs as such in the field^{23–25}. In principle the transgenic approach is more precise and avoids the time consuming processes that accompany hybridization-based breeding. The vast majority of genetically modified (GM) crops on the market provide traits like pest and/or herbicide resistance²⁶, whereas among the major crops only one GM stress resistant variety of corn has been approved by the US Department of Agriculture thus far²⁷. The difficulties could be multi-fold. The complex genetic structure of stress resistance makes finding the correct combination of genes and alleles difficult; the severity, timing and duration of stresses may vary from year to year and location to location, making it harder for the single- and even multiple-gene transgenic approach to prevail. The regulatory burden also makes it difficult to commercialize GM crops²⁵.

Despite the complicated gene–environment interactions that seem difficult to unravel, natural selection has already produced a plethora of stress-resistant plants that are adapted to all types of harsh environments on Earth. Studies of some of these naturally stress-resistant plants (NSRPs) have already provided interesting clues about how to increase stress resistance²⁸. Many of the first crops domesticated by humans are NSRPs. In this Review Article, we briefly review different types of NSRPs that have the potential to be used as crops or as model organisms to inform and guide research on increasing stress resistance in other crops. We hope to demonstrate that recent technological advancements would enable rapid genetic improvements in NSRPs, using some stress-resistant cereal or pseudocereal crops as examples. Such genetic improvements would significantly increase the yield of those that are already crops and to quickly domesticate the wild ones. The genetically improved NSRPs can be integrated into the current intensification systems or used as main crops in areas where they are best suited for. By facilitating the efficient use of marginal land and by diversifying agriculture and the human diet, these future stress-resistant crops will have major positive effects on food security and human health.

Naturally stress-resistant plants

Plants have evolved to grow in virtually every type of terrestrial environment on earth. Many NSRPs thrive in harsh environments that are inhospitable for most other plants. NSRPs that sustain themselves under the most stressful conditions are sometimes called extremophile plants or extremophytes (Box 1). Many well-known NSRPs such as cacti (Cactaceae) and mangroves (Rhizophoraceae) are extremophytes. Extremophytes are worth studying as they may have unique mechanisms conferring high levels of stress resistance, and understanding these mechanisms may help to improve stress resistance of crops. Some of these plants tolerate extreme stresses by radically changing their morphology, physiology and/or metabolism. Most cacti, for example, develop degenerated leaves (spines), succulent stems (cladodes) and widespread shallow root systems. Mangroves have highly suberized roots that exclude most salts, and leaves with glands that secrete excessive salts²⁹. Although some of the specialized traits of extremophytes may be undesirable in regular crops (for example, degenerated leaves and a high accumulation of salt that needs to be removed before animal consumption),

Box 1 | Types of extremophytes

The groupings and terms used below are intended to familiarize the reader with extremophytes rather than to provide precise definitions. The groupings are not mutually exclusive; for example, a plant can be both a xerophyte and a halophyte.

Xerophytes and hydrophytes

Plants that are adapted to an environment with little and abundant liquid water, respectively. Common xerophytes include cacti and the pineapple. Hydrophytes are also called aquatic plants; common hydrophytes include water lilies and liverworts. The plants that live in an environment with medium level of water are called mesophytes.

Resurrection plants

Also called desiccation-tolerant plants, this category contains only a small number (~135) of angiosperm species; most resurrection plants are bryophytes and lichens.

Halophytes

Plants that can grow in the presence of high salt. Halophytes can be technically defined by an arbitrary concentration of salt that a plant can tolerate. For example, Flowers and Colmer define halophytes as plants that can complete their life cycles in the presence of >200 mM sodium chloride⁴⁹. Plants that cannot tolerate this level of salinity are called glycophytes.

Secretahalophytes

Halophytes that contain glandular structures that secrete salt. Mangroves are secretahalophytes.

Cryophytes and thermophytes

Plants that are adapted to environments with very low and very high temperatures, respectively.

understanding the mechanisms and evolution of these traits could provide new perspectives and fresh ideas on how to engineer other plants to be stress resistant.

Stress resistance is a relative concept. Many plants, for example, are more drought resistant than rice but are not as drought resistant as sorghum. If the resistance of all plants to a particular stress were comparatively quantified with consistent measurements, the results would presumably represent a continuum³⁰. It follows that, in defining NSRPs and extremophytes, researchers must draw an arbitrary line along that continuum. Historically, a technical definition has been given only for halophytes, that is, for plants adapted to high salinity conditions (Box 1). That halophytes have been technically defined might possibly result from the fact that soil salinity levels often remain relatively constant throughout a plant's life cycle under natural conditions with exceptions like estuaries. Also soil salinity is more tractable than many other environmental stresses in the laboratory. This type of technical definition is not available (or feasible) for other types of NSRPs or extremophytes. However, the approximate numbers of extremophytes are large. Because of space constraints, we review here only a few groups of NSRPs with very high levels of drought and/or salt stress resistance and with special characteristics that draw the interest of researchers.

Plants that can resist extreme drought conditions, or xerophytes (Box 1), are usually found in typical deserts, where precipitation is defined as less than 25 centimetres per year. Such xerophytes include plants from diverse lineages³¹. Most have developed mechanisms to reduce water usage and to avoid extended dry periods. Resurrection plants, a group of desiccation-tolerant plants, have been the focus of much research. Their vegetative tissues can tolerate up to 95% water loss and can regain all functions after rehydration³². At least 135 angiosperm species belonging to 13 largely unrelated families are

Table 1 | Selected NSRPs that have a reference genome

Species	Common name	Family	Genome size (Mb)	Year published	Type	Reference
<i>Manihot esculenta</i>	Cassava	Euphorbiaceae	742	2014	Drought resistant	107
<i>Setaria italica</i>	Foxtail millet	Poaceae	401	2012	Drought resistant	65,66
<i>Oryza glaberrima</i>	African rice	Poaceae	316	2014	Drought resistant	108,109
<i>Oryza longistaminata</i>	Red rice	Poaceae	347	2015	Drought resistant	110
<i>Pennisetum glaucum</i>	Pearl millet	Poaceae	1760	2017	Drought resistant	68
<i>Chenopodium quinoa</i>	Quinoa	Amaranthaceae	1482	2017	Halophyte	70,72
<i>Amaranthus hypochondriacus</i>	Grain Amaranth	Amaranthaceae	466	2016	Halophyte	73
<i>Eutrema salsugineum</i>	Salt cress	Brassicaceae	260	2012	Halophyte	53,54
<i>Eutrema parvulum</i>	Salt cress	Brassicaceae	140	2011	Halophyte	55
<i>Oryza coarctata</i>		Poaceae	665	2017	Halophyte	111
<i>Rhizophora apiculata</i>	Mangrove	Rhizophoraceae	274	2017	Halophyte	NCBI
<i>Boea hygrometrica</i>	-	Gesneriaceae	1690	2015	Resurrection	40
<i>Oropetium thomaeum</i>	-	Poaceae	245	2015	Resurrection	39
<i>Xerophyta viscosa</i>	-	Velloziaceae	295	2017	Resurrection	41
<i>Solanum commersonii</i>	-	Solanaceae	830	2015	Salt resistant	112
<i>Ananas comosus</i>	Pineapple	Bromeliaceae	526	2015	Xerophyte	113
<i>Populus euphratica</i>	Desert poplar	Salicaceae	593	2013	Xerophyte	114

recognized as resurrection plants³³, and ~300 resurrection angiosperm species are thought to exist³⁴. In response to dehydration, these plants enter extreme dormancy and accumulate antioxidants, sugars and protective proteins such as late embryogenesis abundant proteins and heat-shock proteins³⁵. In addition, they are able to quickly reduce energy expenditure and to inhibit dehydration-induced apoptosis and senescence while inducing autophagy in response to drought stress^{36–38}. The reference genomes have been sequenced for three resurrection plants, including *Oropetium thomaeum*³⁹, *Boea hygrometrica*⁴⁰ and *Xerophyta viscosa*⁴¹ (Table 1). The three genomes vary in size (245 to 1,691 Mb), repeat DNA content (18% to 74%) and gene number (25,425 to 49,374). It follows that none of these features are correlated with desiccation tolerance. On the other hand, transcriptome analyses of different resurrection plants have identified upregulated seed-maturation-related processes, including abscisic acid signalling during dehydration^{40–42}, supporting the hypothesis that resurrection plants gained desiccation tolerance in part by adapting the desiccation-tolerance strategies found in seeds⁴³.

Among the many types of extremophytes, halophytes are the best documented (Box 1). More than 6% of the world's land area is salt affected⁴⁴, while ~0.25% of angiosperm species are estimated to be halophytes⁴⁵. The eHALOPH database contains ~1,400 confirmed halophytic species⁴⁶. Halophytes are distributed in ~500 genera of flowering plants in virtually all families, and most occupy the 'tip' of the phylogenetic tree, suggesting that salt resistance was gained and lost at high frequency during evolution⁴⁷. Despite this diverse phylogenetic distribution, some lineages such as the Chenopodiaceae contain a large number of halophytes. These lineages may contain particular background traits (so called 'enabling traits') that facilitate the evolution of salt resistance. In addition, certain traits such as C₄ photosynthesis were found to be likely associated with salt resistance in grasses⁴⁸. Although all halophytes have the common need for osmotic adjustment and for reducing the toxicity of sodium and chloride ions, the physiology of salt resistance in different halophytes is diverse. Halophytes differ in particular traits such as succulence, the solutes accumulated, and the Na⁺/K⁺ ratio⁴⁹.

A. thaliana has been an excellent model for studying many plant traits including abiotic stress resistance, but researchers have been

searching for alternative model organisms that are naturally adapted to stressful environments⁵⁰. Nearly 20 years ago, a halophytic relative of *A. thaliana*, salt cress, was chosen as a model for molecular genetics studies⁵¹. Salt cress belongs to the former *Thellungiella* genus, which contains four species²⁸. Among them, *Eutrema salsugineum* (formerly *Thellungiella halophila* or *Thellungiella salsuginea*) is the best characterized and can resist seawater-level salinity as well as cold, drought and low-nitrogen stress²⁸. The high level of salt resistance of this species is attributed to its excellent ion homeostasis, high concentrations of compatible solutes, and low transpiration under high-salt conditions^{28,50}. In addition, the plant exhibits a constitutively high level of expression of genes involved in the regulation of the above processes, indicating that the plant is pre-conditioned to accommodate salt-stress environments²⁸. Interfering with the function of SOS1 (SALT OVERLY SENSITIVE 1) and other ion transporters leads to the loss of salt resistance in *E. salsugineum*⁵². Thus, the same molecular machinery responsible for salt resistance in *A. thaliana* is also necessary for salt resistance in salt cress. The genomes have been sequenced for two salt cress species, *E. salsugineum* (Shandong ecotype)^{53,54} and *Eutrema parvulum* (formerly *Thellungiella parvula*)⁵⁵ (Table 1), which have estimated genome sizes of 243 Mb and 140 Mb and repeat DNA contents of 51.4% and 7.5%, respectively. The high value for *E. salsugineum* repeat DNA content indicates that the activity of transposable elements was mainly responsible for its genome expansion. The two genomes show strong synteny to the *A. thaliana* genome and contain similar numbers of protein-coding genes to *A. thaliana*^{53–55}. Compared to *Arabidopsis*, the two *Eutrema* genomes contain a tandem duplication of certain salt-responsive genes and miRNAs together with copy number expansion of specific gene families^{53,55}. Because none of these genomic features is sufficient to explain salt resistance in these halophytes, researchers have proposed that the adjustment of the regulatory network of stress response is important for their adaptive evolution^{53,54}.

Domesticated stress plants

Determining which NSRPs warrant study is not straightforward. If we attempt to select and study NSRPs whose main habitat is significantly more stressful than the crop field, the number of such

plants is too high. From a practical point of view, we should focus on those NSRPs that have a suite of desired features, including food and economical traits, that is, non-toxic, nutritious, culturally important, ecologically friendly, and so on. It was estimated that 20,000–75,000 plant species are edible^{56,57}, while 2,500–7,000 plant species have been cultivated for food in human history⁵⁸. We should further focus on those NSRPs with relatively close evolutionary relationships with current major crops. Then the knowledge we have learned about improving yields of major crops can be applied to these NSRPs relatively easily and the mechanisms underlying the extreme stress resistance of these NSRPs can help improve stress resistance of major crops in the long run.

Many of the early domesticated plants can be classified as NSRPs, and some are also relatives of current major crops. They were domesticated because they had reasonable yield in the early history of human culture when irrigation, fertilizers and pesticides were not available⁵⁹. Over the past half a century, the cultivation of many of the crops has dramatically declined. These so-called minor crops, or orphan crops, however, hold substantial potential to increase global food security. Compared to the major crops, they use water or soil nutrients more efficiently or are more resistant to diseases and pests, and are thus more sustainable. Most of these minor crops have not been subjected to intensive breeding efforts and can be considered not fully domesticated, which implies that small genetic improvements may greatly increase their yield^{60,61}. The lack of intensive single-purpose breeding efforts also indicates that the current collection of cultivars of these minor crops still contain large genetic diversity, which can be utilized to improve their yield while maintaining their stress resistance. In the following paragraphs, we list a number of minor crops that cope well with different stresses, especially with drought and salt stresses.

A group of C_4 cereals called millets are drought resistant. Millets are small-seeded annual crops that belong to multiple genera of the grass family. Millets usually include pearl millet (*Pennisetum glaucum*), finger millet (*Eleusine coracana*), foxtail millet (*Setaria italica*), kodo millet (*Paspalum scrobiculatum*), broomcorn millet (*Panicum miliaceum*), barnyard millet (*Echinochloa esculenta* and *Echinochloa frumentacea*, Japanese and Indian varieties respectively), fonio millet (*Digitaria exilis*), and little millet (*Panicum sumatrense*). Among all cultivated cereals, millets rank sixth based on annual production. All millets are drought resistant and are adapted to temperate, subtropical, and/or tropical regions. Currently, more than 95% of millet production is from Asian and African countries, where millet serves as a staple food⁶². In addition to being drought resistant, millets are typically salt resistant and require little nitrogen fertilization. Stress resistance varies among millet species as well as among cultivars of the same species. Broomcorn millet, for example, has the highest water-use efficiency among all cultivated cereals and produces grains in areas with less than 400 mm of annual precipitation⁶³, whereas barnyard millet has excellent nitrogen-use efficiency⁶⁰. The main factors preventing wide cultivation of millets include low yields and lack of cultivars bred for different regions. Foxtail millet is an example that demonstrates the potential of these stress-resistant crops. First domesticated in China at least 8,700 years ago, foxtail millet is historically one of the most important crops in Northern China. Since the 1960s, researchers in China have been breeding new cultivars of foxtail millet. In 2007, the hybrid foxtail millet cultivars bred by the Zhangjiakou Institute of Agricultural Sciences achieved an average yield of 7,500 kg ha⁻¹ and a record yield of >12,000 kg ha⁻¹ with irrigation⁶⁴. As the value of millets is increasingly recognized, genomic resources are being generated for their further improvement (Table 1). The genome sequences and high-density linkage maps of two Chinese cultivars of the foxtail millet and resequencing data for 916 foxtail varieties have been published^{65–67}. In 2017, the reference genome of pearl millet together with the resequenced genomes of 994 cultivars were published⁶⁸.

These data, combined with germplasm resources⁶⁰, are expected to accelerate the genetic improvement of millets.

The Chenopodioideae subfamily contains the largest number of halophytic species⁴⁷. One halophytic crop from this subfamily, *Chenopodium quinoa*, has gained substantial attention in recent years. Quinoa can tolerate up to seawater-level salinity, and the salt resistance varies among ecotypes. Most cultivars achieve highest biomass at intermediate salinity levels⁶⁹. Domesticated ~7,000 years ago in the Andean regions of South America, quinoa is adapted to a wide range of climate niches in this mountainous terrain. Hence, it also exhibits strong resistance to cold, drought and low soil nitrogen⁶¹. Quinoa is now mainly produced in Peru, Bolivia, Ecuador and other South American countries, but its cultivation expanded from eight countries in 1980 to 75 countries in 2014 (ref. ⁶¹). Three reference genome sequences of quinoa have been published^{70–72}. The two more recent assemblies mainly used single-molecule long reads and have significantly better contiguity for this tetraploid genome^{70,72}. These two sequenced varieties represent the coastal⁷² and the highland⁷⁰ ecotypes of quinoa. Similar to some millets, quinoa is in a ‘semi-domesticated’ state, and current cultivars often do not grow uniformly in the field. To promote the cultivation of quinoa, high-yielding varieties and cultivars suitable for regions outside the Andes are needed.

We should also consider several other pseudocereals from the order Caryophyllales, such as grain amaranth⁷³ (*Amaranthus hypochondriacus*), kaniwa (*Chenopodium pallidicaule*) and buckwheat^{74,75} (*Fagopyrum esculentum* and *Fagopyrum tataricum*). These pseudocereals, buckwheat in particular, are known to tolerate nutrient deprivation and other stresses, and have considerable health benefits to humans^{74,75}. Africa also has a large number of stress-resistant crops that are poorly documented in the literature, and the African Orphan Crops Consortium plans to generate genomic resources for 101 important orphan crops grown in Africa⁷⁶. With more genomic information now available for these stress-resistant crops, international frameworks that coordinate the exchange of germplasms are needed, because most germplasm resources for the orphan crops are restricted to their original countries. In addition, more efforts are needed to preserve wild relatives of these crops because they are now significantly underrepresented in seed banks and much of the biodiversity are under threat of extinction⁷⁷. At the same time, we should not limit ourselves to the above listed stress-resistant crops, which were selected by our ancestors thousands of years ago. With the current knowledge of the phylogeny of NSRPs and the genetic basis of crop domestication, we should be able to identify many more NSRPs that are suitable for domestication.

NSRPs help diversify agriculture and the human diet

It is clear that stress-resistant crops can increase food security by adding diversity to modern agriculture. Three major crops (maize, wheat and rice) currently account for about 50% of the world's consumption of calories and protein, and about 95% of the world's food needs are provided by just 30 species of plants⁵⁸. Crop biodiversity has significantly decreased during the past several decades, reflected in the decrease in both the number of crop species being cultivated and the biodiversity within major crops⁷⁸. The resulting homogeneity in the elite varieties and their wide cultivation makes modern agriculture highly vulnerable to pathogen outbreaks and/or extreme weather and soil conditions⁷⁹. To overcome these drawbacks, more sustainable farming systems (such as sustainable intensification, ecological intensification and organic farming) have been proposed and are being explored⁸⁰. These new systems aim to maintain the high productivity of conventional intensified agriculture and to minimize its environmental harms. The practices differ but usually involve intercropping, crop rotation, reduced tillage, and so on⁸⁰. Studies found that including broomcorn millet in multiple rotation systems in the United States helps with weed control,

disease/insect management and/or soil moisture preservation⁶². In its countries of origin, quinoa following potato cultivation or intercropping with beans, tarwi and corn is also recommended to benefit quinoa yield and pest control⁸¹. Thus, it is feasible to integrate these stress-resistant crops into current agricultural systems and provide benefits in sustainability.

Another reason for using more stress-resistant crops is to help diversify the human diet. Humans consume a much larger menu of plants in many developing countries, including China and India, than in developed countries. These edible plant resources should be protected and enhanced. During the past half century, food quantity and food diversity in some countries has increased⁸², mainly because of globalization. At the same time, however, the supply of minor crops has declined and the food supply has become more homogeneous globally⁸². Global dietary preferences have shifted towards Western diets, which feature meat and dairy, sugary beverages and wheat products⁸². Although high-carbohydrate diets are associated with increased risks of many chronic illnesses, our current major crops are rich in carbohydrates⁸³. In addition, global climate change not only affects crop yields but also reduces the nutritional value of major crops⁸⁴. Stress-resistant crops such as millets and quinoa are superior food sources because, compared to rice, wheat and maize, they have higher contents of dietary fibre, proteins and minerals and lower levels of carbohydrates^{85,86}. To cope with stressful environments, stress-resistant crops have to accumulate distinct secondary metabolites, many of which are beneficial for humans. The grains of both quinoa and millet, for example, are rich in phenolic compounds with antioxidant activity^{85,86}. Chinese traditional medicine emphasizes 'homology of medicine and food', which means that many foods have medicinal values and that their long-term consumption can help treat specific illnesses, especially chronic diseases. The importance of diet is also reflected by recent research on cancer cell metabolism⁸⁷, and on how the simple control of dietary nutrients may help treat and even prevent cancer^{88,89}. As obesity and diabetes become pandemic globally⁹⁰, we need to produce food with more diversity and more balanced nutrients in the future.

Strategies and tools for the utilization of NSRPs

We propose that fast genetic improvement of yield in naturally stress-resistant crops can be achieved by combining the knowledge of domestication genetics and rapidly developing techniques, such as high-throughput sequencing, genome editing and plant transformation (Fig. 1). Different from our ancestors, we can try to consciously maintain stress resistance and the nutritional value when we make genetic improvements for increased yield. During the domestication of different crop species, similar traits were selected for, such as reduced seed shattering, determinate growth and larger seed size. This phenomenon was called the 'domestication syndrome'⁹¹. Orthologous genes were found to be involved in the domestication of different species, especially for species that are phylogenetically close⁹². For example, loss-of-function mutations in orthologous genes of *Arabidopsis TFL1* (*TERMINAL FLOWER 1*) resulted in determinate growth in both Solanaceae (tomato) and Fabaceae (soybean and common bean)⁹², which is also a desired trait for mechanized harvesting of many crops. Changes in orthologous genes involved in gibberellin metabolism/signalling underlie the semi-dwarfism trait that drove the Green Revolution in multiple cereals⁹³. Considering the highly conserved function of gibberellins in plants, similar changes can be applied to other cereal or pseudo-cereal crops to help improve their yield. Among the many QTLs that control grain size, grain weight or grain number in different cereals, several genes were also found to be conserved⁹¹, so they are potentially useful for improving yield of NSRPs from the grass family. Although the antagonistic relationship between plant growth and stress response is well known, none of the above mentioned high-yield alleles were found to negatively affect stress response. Thus it

should be feasible to increase yield while maintaining stress resistance in NSRPs.

The precise editing of genes of stress-resistant plants requires well-annotated reference genomes. The cost of next-generation sequencing has decreased by more than 1,200-fold over the past 10 years⁹⁴. As a result, mRNA sequencing has replaced the microarray as the preferred method for transcriptome profiling, and de novo sequencing of a medium-sized genome is becoming possible for individual laboratories. In particular, the single-molecule sequencing by PacBio Biosciences or Oxford Nanopore Technologies can now deliver an average read length of >10 kb and a maximum read length of >50 kb, which makes this type of sequencing ideal for de novo genome assembly⁹⁵. A significant technical limitation is the error rate, which is ~15% for both technologies and can only be mitigated by high sequencing depth⁹⁵. Short-read sequencing, on the other hand, has an advantage in lower sequencing cost and is ideal for applications such as genome resequencing and transcriptome profiling. More and more algorithms are being developed to better exploit the unique properties of different sequencing technologies, and recently published plant genomes usually have good completeness and contiguity^{96,97}. The high-quality assembly, when combined with a genetic map, can provide a solid foundation for molecular breeding and genome editing in NSRPs.

Traditional breeding methods rely on hybridization and recombination to stack favourable alleles together. This process is usually time consuming and labour intensive, especially when the crop is not fully domesticated or is newly domesticated. The genome editing technique allows simultaneous modification of multiple genes in one or two generations and is thus ideal for assembling multiple desirable alleles in the same genetic background. The CRISPR-Cas9-based system is currently the prevalent genome-editing tool in plants. Adapted from bacterial immune systems, CRISPR-Cas9 stands for clustered regularly interspersed short palindromic repeats-CRISPR-associated protein 9 (ref. 98,99). The system has two components: the single-guide RNA (sgRNA), which recognizes the target sequence through base pairing, and the DNA endonuclease Cas9, which binds to sgRNA and cleaves the genomic DNA⁹⁹. After the cleavage, double-strand breaks (DSBs) in plants are mainly repaired through the error-prone non-homologous end-joining pathway, which usually results in small insertions or deletions at the DSB site. Thus, CRISPR-Cas9 can efficiently knock-out a gene if the sgRNA is designed to target the coding sequence. Gene knock-in or replacement using CRISPR-Cas9 and donor DNA as the DSB repair template has also been reported for several plant species⁹⁹. It utilizes the homology-directed repair (HDR) pathway, but currently suffers from low efficiency due to the poor HDR activity in plant cells. A recent study has achieved efficient gene targeting in *Arabidopsis* using Cas9 driven by an egg cell- and early embryo-specific promoter¹⁰⁰. Using an inactivated or partially inactivated Cas9 fused to a cytidine deaminase or an adenine deaminase, several groups recently achieved C to T or A to G base conversion^{99,101}. In summary, the CRISPR toolbox can be used to precisely edit plant genomes, although some technical limitations remain.

Transformation is another main hurdle that prevents the genetic modification of many plant species. Two recent studies suggest that we may be close to achieving genotype-independent transformation in plants. The first study showed that overexpression of two maize transcription factors, *Bbm* (*Baby boom*) and *Wus2* (*Wuschel2*), improved transformation in monocots such as sorghum, sugarcane, indica rice and maize, including previously non-transformable maize lines¹⁰². *BBM* and *WUS* were called morphogenic genes because overexpression of either one can induce somatic embryogenesis in *Arabidopsis*¹⁰². Overexpression of orthologous morphogenic genes may similarly increase the transformation efficiency of NSRPs. In another study, DNA-coated magnetic nanoparticles were delivered into cotton pollen through pollen apertures, which are

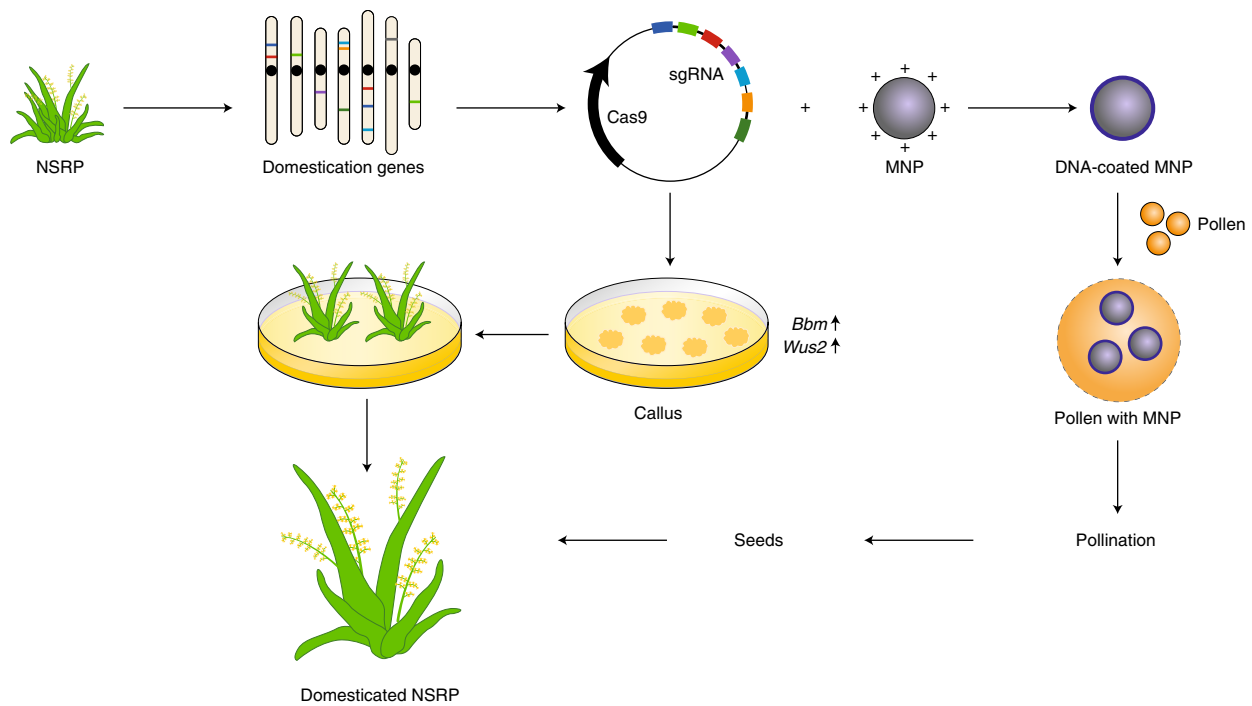


Fig. 1 | The rapid domestication of NSRPs using precise gene editing. After the reference genome (or assembled transcriptome) of an NSRP is generated, candidate domestication genes can be identified based on their orthologous relationship with domestication genes in the closest crop relative. A CRISPR-Cas9 vector targeting multiple candidate domestication genes can then be generated. CRISPR-Cas9 can be delivered into the plants in at least two ways: (1) the plasmid can be delivered into calli (for example, through particle bombardment), with co-delivery of a plasmid for overexpression of *Bbm* and *Wus2* orthologous genes to facilitate plant regeneration; or (2) the plasmid DNA or Cas9-sgRNA ribonucleoprotein complex can be mixed with magnetic nanoparticles (MNPs), and the coated MNPs can then be drawn by a strong magnetic field into pollen through pollen apertures. The magnetofected pollen is used to pollinate emasculated flowers to generate gene-edited plants. Edited NSRPs with desired traits can then be selected in the field or glasshouse.

cell-wall-free openings present on almost all pollen¹⁰³. The authors showed that genomic integration of the delivered DNA could be detected in the T_1 generation and that the integrated DNA was stably inherited in later generations¹⁰³. If sufficiently reproducible, nanoparticle-based methods may allow the easy and rapid transformation of any flowering plant species without the need for tissue culture and plant regeneration¹⁰⁴.

In summary, combining the tools of high-throughput sequencing, genome editing and efficient transformation methods would allow the precise editing of domestication genes in NSRPs. This will result in the rapid domestication of these plants. This process of ‘molecular domestication’ can be accelerated by ‘speed breeding’, a strategy that can ensure six generations of wheat within 1 year by manipulation of lighting, temperature and day length, as well as by the use of embryo rescue and rapid seed drying to shorten the plant life cycle¹⁰⁵. These tools can also be used for the rapid breeding of the previously mentioned minor crops. In addition, the NSRPs can benefit from other modern breeding technologies such as marker-assisted selection, genomic prediction and high-throughput phenotyping.

Conclusion

In his Nobel lecture, Norman Borlaug, the ‘father of the Green Revolution’, described the Green Revolution as “A temporary success in man’s war against hunger and deprivation; it has given man a breathing space”¹⁰⁶. To succeed in the long term, we must now develop an agriculture that is both sustainable and sufficiently productive to keep pace with the growth of the human population. Breeding for high yield in naturally stress-resistant crops complements current efforts in breeding stress resistance in major crops. Preliminary efforts indicated that some NSRPs have great potential in yield growth and there can be mutual benefits with major crops

when used in various intercropping and/or crop rotation systems. Considering the large number of NSRP species, significant efforts are needed to systematically search for suitable crops, to develop corresponding techniques for genetic improvements in yield, and to explore appropriate agronomic practices. For better food security and a healthier diet, the world needs many more stress-resistant crops. As both researchers and global citizens, we look forward to a sustainable future with many stress-resistant, resource-efficient and nutrient-diverse grain, vegetable and fruit crops.

Received: 12 December 2017; Accepted: 17 October 2018;
Published online: 26 November 2018

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Acknowledgements

We would like to thank H. Zhang and R. Bressan for careful reading and editing of the manuscript. Research funding was provided by the Chinese Academy of Sciences (CAS) to J.K.Z. and by Strategic Priority Research Program of the Chinese Academy of Sciences (XDB27040108), Shanghai Science and Technology Committee (17391900200), Youth Innovation Promotion Association of CAS (2014242), National Key R&D Program of China (2016YFA0503200) and CAS to H.Z.

Author contributions

H.Z. and J.K.Z. wrote the paper; H.Z. and Y.L. analysed data.

Competing interests

The authors declare no competing interests.

Additional information

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